# Acylaminoacetyl Derivatives of Active Methylene Compounds. 1. The Cyclization of the Benzoylaminoacetyl Derivatives to α-Substituted Tetramic Acids (1)



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Hippuric acid was converted to α-Y-substituted tetramic acids (Y = -CN, $-CO_2R$ and $-COCH_3$) according to the following general scheme of reactions: a) preparation of the hippuric acid chloride or of its *p*-nitrophenyl ester; b) *C*-acylation of an active methylene compound $Y-CH_2-CO_2R$ using the acid chloride or the active ester; and c) intramolecular condensation of the *C*-acylation compound to an α-Y-substituted tetramic acid. The conditions of the *C*-acylation reaction and the structure and reactivity of the benzoylaminoacetyl derivatives were investigated.

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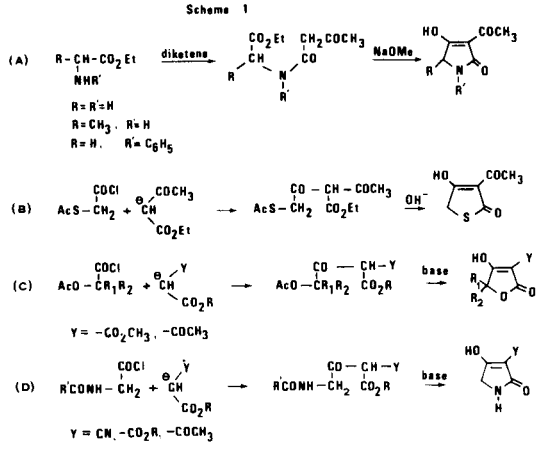
## Introduction.

A general method for the synthesis of α-acetyltetramic acids (2), developed in 1954 by Lacey (3), consists in the preparation of the *N*-acetoacetyl derivatives of α-amino acid esters, which are then cyclized by an intramolecular Claisen condensation reaction (Scheme 1, A). The method has since been used for the synthesis of various γ-substituted α-acetyltetramic acids starting with different α-amino acids (4-7) and has been extended to the synthesis of α-cyano- (5) and α-carbalkoxytetramic acids (5, 8-12). A similar reaction sequence was also developed by Lacey (13) for the conversion of α-hydroxy acid esters to α-acetyltetronic acids. The method could not, however, be applied to the synthesis of the corresponding thiotetronic acids (13).

Scheme 1




α-Acetylthiotetronic acid had already been prepared by Benary (14) through reaction of sodium acetoacetate with *S*-acetylthioglycolic acid chloride and subsequent cyclization, with simultaneous deacetylation, of the resulting *C*-acylation compound in alkaline medium (Scheme 1, B). This reaction scheme, which has been used recently (15) for the synthesis of α-benzoyl- and α-butyrylthiotetronic acids, is essentially an application of a general method of synthesis of α-substituted tetronic acids (Scheme 1, C; Y = $-CO_2CH_3$ and $-COCH_3$) devised by Benary (16,17) and Anschütz (18-20).

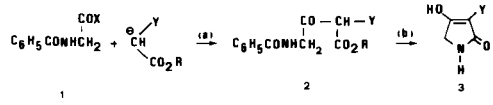
An extension of this method to the synthesis of α-substituted tetramic acids would require the cyclization of acylaminoacetyl derivatives of active methylene compounds (Scheme 1, D; Y = -CN, $-CO_2R$, $-COCH_3$). As a preliminary investigation of this reaction scheme, we describe here the synthesis and cyclization of the benzoylaminoacetyl derivatives (R' = $C_6H_5$). A literature search revealed that reaction of hippuryl chloride with ethyl sodiocyanoacetate and sodiomalonate in anhydrous ether was shown (21) to yield the corresponding *C*-acylation compounds, ethyl hippurylcyanoacetate and ethyl hippurylmalonate, respectively. However, conversion of these esters to the corresponding α-substituted tetramic acids had not been reported; it had even been stated (22) that the intramolecular condensation of ethyl hippurylmalonate to α-carbethoxytetramic acid was not possible.

## Results and Discussion.

Reaction of hippuryl chloride (**1a**) with the anions of the active methylene compounds $Y-CH_2-CO_2R$ was actually found to proceed to the corresponding benzoylaminoacetyl derivatives **2a-2f** (Scheme 2). Typical experimental conditions consisted in the reaction of the chloride **1a** (1 mole) with the anion generated from the action of a base, potassium *t*-butoxide in *t*-butyl alcohol or sodium hydride in benzene (2 moles), on the active methylene compound (3 moles), at room temperature for 2-3 hours. The *C*-acylation compounds **2a-2f** could be isolated in better than 50% yields either as crystalline solids (**2a-2e**) or as an oily product (**2f**) which was purified through column chromatography. The *C*-acylation reaction was then found to proceed equally well starting with the *p*-nitrophenyl ester **1b** under the same experimental conditions. It should be noted that the reaction of the chloride **1a** with

methyl or ethyl acetoacetate is only possible with sodium hydride in benzene, since the reaction with potassium *t*-butoxide in *t*-butyl alcohol resulted in the isolation of hippuric acid. However, the reaction of the *p*-nitrophenyl ester **1b** with the two acetoacetate esters was found to proceed with either base.

Scheme 2



**1a**, X = Cl
**1b**, X = $-OC_6H_4NO_2$-*p*

**2a**, Y = CN, R = Me
**2b**, Y = CN, R = Et
**2c**, Y = $CO_2Me$, R = Me
**2d**, Y = $CO_2Et$, R = Et
**2e**, Y = $COCH_3$, R = Me
**2f**, Y = $COCH_3$, R = Et

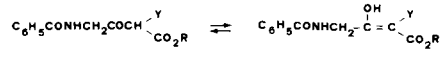
**3a**, Y = CN
**3b**, Y = $CO_2Me$
**3c**, Y = $CO_2Et$
**3d**, Y = $COCH_3$

(a) One mole of **1**, 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. (b) Refluxing **2** with two equivalents of NaOMe/MeOH (for Y = -CN) or NaOEt/EtOH-$C_6H_6$ (for Y = $-CO_2R$) or NaOMe/MeOH-$C_6H_6$ (for Y = $-COCH_3$).

The $C_6H_5CONHCH_2$- moiety of the *C*-acylation compounds **2a-2f** is apparent from their pmr spectra in deuteriochloroform solution (Table 1), which exhibit the methylene -$NHCH_2$-signal as a doublet J ≅ 5-6 cps, due to the coupling with the -NH- amide proton. These compounds are either exclusively in the enolic form, for Y = -CN and $-COCH_3$ (**2a**, **2b**, **2e** and **2f**), or mixtures of the enolic and keto forms, for Y = $-CO_2R$ (**2c** and **2d**). Indeed, only the carbalkoxy derivatives, **2c** and **2d**, exhibit a methine -$CHYCO_2R$ singlet, at δ 4.76 and 4.62 ppm respectively, together with an enolic proton signal at low field, ~ 14 ppm. Moreover, the $-CO_2R$ protons of **2c** and **2d** appear as two different signals, corresponding to the keto and enol forms. It has been reported (23) that, in keto-enol mixtures of β-ketoester derivatives, the ester $-CO_2R$ protons of the two forms appear in different chemical shifts, the signals of the keto form in higher field than those of the enolic form. From the relative intensities of the $-CO_2R$ signals, the enolic form was estimated to 28% for **2c** and 38% for **2d**.

Table 1

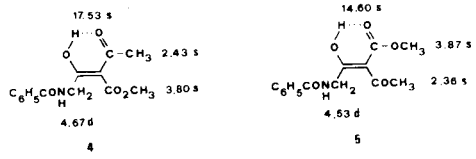
PMR Spectra (a) of the Benzoylaminoacetyl Derivatives **2**



| Compound (b) | $-CO_2R$ | N-$CH_2$- | $C_6H_5CO$- | -$CHYCO_2R$ | -NH- | -OH |
|---|---|---|---|---|---|---|
| **2a** (c) | 3.86<br>s, 3H | 4.55<br>d (6), 2H | 7.40-7.97<br>m, (5H) (d) | | 7.20<br>m, (1H) (d) | |
| **2b** (c) | 1.37<br>t (7), 3H<br>4.35<br>q (7), (2H) (e) | 4.56<br>d (6.5), (2H) (e) | 7.40-8.02<br>m, (5H) (f) | | 7.21<br>m, (1H) (f) | 12.90<br>br, ≅0.7 H |
| **2c** | 3.84 (K) and 3.86 (E)<br>two s, 6H (g) | 4.55<br>d (5), (2H) (h) | 7.36-7.95<br>m, (5H) (i) | 4.76<br>s, (≅1H) (h) | 6.95<br>m, (1H) (i) | 14.30<br>s, (≅0.2H) (h) |
| **2d** | 1.31<br>t (7), 6H<br>4.28<br>q (7), (4H) (j) | 4.55<br>d (5), (2H) (j) | 7.36-7.95<br>m, 5H | 4.62<br>s, (≅1H) (j) | 6.95<br>m, 1H | 14.20<br>s, (≅0.2H) (j) |
| **2e** (k) | 3.80<br>s, 3H | 4.67<br>d (5), 2H | 7.30-7.87<br>m, (5H) (ℓ) | | 7.17<br>m, (1H) (ℓ) | 17.53<br>s, 1H |
| **2f** (m) | 1.38<br>t (7)<br>4.35<br>q (7) | 4.75<br>d (5), 2H | 7.40-8.06<br>m | | 7.20<br>m | 18.50<br>s, 1H |

(a) In chloroform solution; the proton signals are given in δ values (ppm) relative to TMS (internal standard) and coupling constants (cps) are given in parentheses. (b) See Scheme 2. (c) Compounds **2a** and **2b** were rather insoluble in deuteriochloroform; it was thus difficult to obtain a clear trace (compound **2a**) or an exact integration (compound **2b**) of the -OH signal. (d)The signals at 7.40-7.97 and 7.20 ppm integrate for 6 protons. (e) The signals at 4.35 and 4.56 ppm integrate for 4 protons. (f) The signals at 7.40-8.02 and 7.21 ppm integrate for 6 protons. (g) Signals of the keto (K) and enol (E) forms respectively. (h) The signals at 4.55, 4.76 and 14.30 ppm integrate for 3 protons. (i) The signals at 7.36-7.95 and 6.95 ppm integrate for 6 protons. (j) The signals at 4.28, 4.55, 4.62 and 14.20 ppm integrate for 7 protons. The methyl (1.31 ppm) and methylene (4.28 ppm) signals of $-CO_2Et$ consist of two overlapping signals of the keto and enol forms, triplets and quartets respectively, whose chemical shifts do not differ more than 1 cps. (k) The signal for $-COCH_3$ appears at 2.43 ppm, s, 3H. (ℓ) The signals at 7.17 and 7.30-7.87 ppm integrate for 6 protons. (m) The signal for $-COCH_3$ appears at 2.48 ppm, s, 3H. This compound contains a small proportion of ethyl acetoacetate, as evidenced from the low intensity singlets at 2.30 ($CH_3CO$-) and 3.58 ppm ($-COCH_2CO_2Et$); integrated values are given only for those signals which are not influenced from the ethyl acetoacetate absorptions. The signals at 7.40-8.06 and 7.20 ppm integrate for 6 protons.

The proton signals -$COCH_3$, -$CO_2CH_3$, N-$CH_2$- and -OH reported in Table 1 for compound **2e** are really accompanied by a second set of lower intensity signals. As indicated in formulae **4** and **5**, the two sets of signals should be attributed to the two possible configurations about the double bond of the enolic structure of compound **2e**. The difference in chemical shifts of the -$COCH_3$ and -$CO_2CH_3$ signals in the two isomers can be assigned to a deshielding of the methyl protons through the intramolecular hydrogen bonds in **4** and **5** respectively. It should also be

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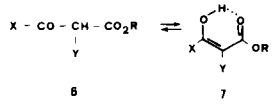
noted that the -OH signal at 14.60 ppm of **5** appears in the same region as for the carbalkoxy derivatives **2c** and **2d** (Table 1). Integration of the two -OH signals shows a relative proportion of **4** to **5** of approximately 9:1.

The enolic structure of compounds **2a-2f** can be correlated to the keto-enol tautomerism of α-Y-substituted β-keto esters **6** (24). The relative proportion of the enolic form **7**




6 7

increases with an electron-withdrawing Y group; in ethyl α-cyanoacetoacetate the enolic form amounts to more than 90% of the mixture (23). On the other hand, the relative proportion of the keto form is favored with an increase in the size of the Y group -$CO_2R$ as compared to -CN in the present case. A strong intramolecular hydrogen bond through the -$COCH_3$ group, as shown in **4**, would stabilize the enolic form in the acetyl compounds **2e** and **2f** and this actually results in a very low field signal for the enolic proton at ~ 18 ppm (Table 1).

The structure of compounds **2a-2f** is further confirmed from their ir spectra in nujol (Table 2), which are characterized by a sharp -NH- band at about 3250-3350 $cm^{-1}$, a CO amide band at about 1660 $cm^{-1}$ and an amide II band at 1520-1540 $cm^{-1}$. The enolic -OH band of the cyano compounds, **2a** and **2b**, is only apparent in chloroform solution at 3450 $cm^{-1}$. Only the carbalkoxy compounds, **2c** and **2d**, in which the keto form is favored, present two strong and sharp bands at 1740-1760 and 1720 $cm^{-1}$ (ester and ketone CO absorptions respectively of the keto form). In agreement with their enolic structures, compounds **2a-2f** give intense, orange to red, colours with an aqueous solution of ferric chloride.

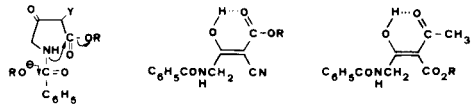
Refluxing the *C*-acylation compounds **2** with an excess, usually two equivalents, of an alkoxide (sodium methoxide in methanol for Y = -CN, sodium ethoxide in ethanol/benzene for Y = -$CO_2R$ and sodium methoxide in methanol/benzene for Y = -$COCH_3$) resulted in the formation of the corresponding α-substituted tetramic acids **3a-3d** (Scheme 2), which were isolated in yields of 40 to 60%. It was found that the cyclization reaction required only 3 hours refluxing for Y = -$CO_2R$ and -$COCH_3$, while for Y = -CN a refluxing of 10 hours was necessary. The intramolecular cyclization reaction **2** → **3** would require a simultaneous debenzoylation step, probably through a concerted mechanism as shown in **8**. Such a mechanism would account for the dif-

Table 2

IR Absorption Bands (a) of the Benzoylaminoacetyl Derivatives **2**


| Compound (b,c) | -OH | -NH- | -CN | ester CO of ketonic β-keto ester | ketone CO of ketonic β-keto ester | ester CO of enolic β-keto ester, amide CO and C=O | amide II |
|---|---|---|---|---|---|---|---|
| **2a** (nujol) | | 3246 m, sh | 2220 m, sh | | | 1660 m, 1640 m | 1530 m |
| (Chloroform) | 3450 sh, w | 3330 w | 2220 m, sh | | | 1660 s, br | 1515 s, br |
| **2b** (nujol) | | 3300 m, sh | 2222 m, sh | | | 1654 s, br, 1645 s, br | 1530 m, sh |
| (Chloroform) | 3450 m | 3333 m | 2220 m, sh | | | 1655 s, br | 1510 m |
| **2c** (nujol) | | 3276 m, sh | | 1760 m, sh | 1724 s, sh | 1640 m, sh | 1540 m, br |
| **2d** (nujol) | | 3311 m, sh | | 1736 s, sh | 1720 s, sh | 1645 m, sh | 1520 s, br |
| **2e** (nujol) | | 3330 br, m | | | 1720 m, br | 1645 m, br | 1520 m, br |

(a) Absorption bands, in reciprocal centimeters, are characterized as of strong (s), medium (m) or weak (w) intensity and as broad (br) or sharp (sh). (b) See Scheme 2. (c) The ir spectrum of compound **2f** is not reported, since a small proportion of ethyl acetoacetate present alters the general absorption pattern.



8 9 10

ference of reactivity of the cyano compounds. Stabilization of these compounds in an enolic form **9** (or its enolate) would require more drastic conditions, as compared to the acetyl compounds **10**, in order to bring the $-CO_2R$ group in a position suitable for a concerted reaction such as **8**.

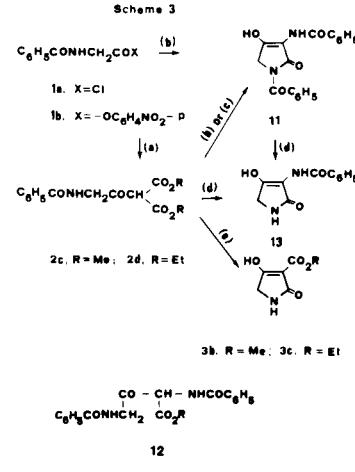
The debenzoylation — intramolecular condensation reaction **2** → **3** can also proceed in an aqueous alkaline solution at room temperature: α-cyano- (**3a**) and α-carbethoxy- (**3c**) tetramic acids could thus be prepared from **2b** and **2d** in 62% and 68% yield respectively. α-Acetyltetramic acid (**3d**) was then prepared without isolation of the *C*-acylation compound, following a procedure described recently (15) for the synthesis of α-acylthiotetronic acids: the chloride **1a** reacted with ethyl sodioacetoacetate in toluene and the *C*-acylation compound was extracted with an aqueous alkaline solution; stirring this solution at room temperature for 3 days and acidification afforded the acid **3d** in 41% overall yield (see Experimental).

The α-substituted tetramic acids **3a-3d** obtained by the present method are known compounds. Their pmr and ir spectra (see Experimental) are consistent with an enolic structure (25). Their ir spectra especially are characterized by a usually sharp -NH- band at 3150 - 3250 $cm^{-1}$, a strong CO lactam band at 1690 - 1710 $cm^{-1}$ and two strong bands at about 1660 and 1620 $cm^{-1}$, CO and C=C respectively of the enolic β-keto ester or β-diketone system. In agreement with their enolic structure, all tetramic acids **3** give intense red colours with an aqueous solution of ferric chloride.

In general, reactions **1** → **2** → **3** proceed satisfactorily under the coniditions reported in Scheme 2, though no attempt has been made to optimize the yields. The cyano compounds **2a** and **2b** can be prepared in equally good yields using the proportions of compound **1** to base to active methylene compound 1:1.1:1.1 instead of 1:2:3. Under these conditions, reaction with malonic and acetoacetic esters results in rather complex mixtures of products.

Reaction of hippuryl chloride (**1a**) or its *p*-nitrophenyl ester (**1b**) with malonic esters at room temperature for 12 hours afforded *N*-benzoyl-α-benzoylaminotetramic acid (**11**) (Scheme 3). Intermediate reaction times, between 3 and 12 hours, resulted in the formation of mixtures of **2c** or **2d** and **11**. Compound **11** could be easily separated from the mixture, since it is insoluble in warm benzene, and was characterized by its ir spectrum and an intense blue-violet colour with ferric chloride (27). Under the same reaction conditions, the *C*-acylation compounds **2c** and **2d** afforded again compound **11**. Since **11** has been obtained by the action of a base, sodium ethoxide or sodium hydride, on either hippuryl chloride (**1a**) or ethyl hippurate (28-30), it should probably derive from an intermediate α-hippuryl-hippuric ester **12** (29). Formation of such an intermediate would require a nucleophilic attack of the excess anion on the ketone carbonyl of the initially formed *C*-acylation compound **2c** or **2d**. This point seems reasonable since compound **13**, derived from debenzoylation of **11** on refluxing with sodium methoxide in methanol, was also obtained from **2c** or **2d** under the same conditions.

Scheme 3

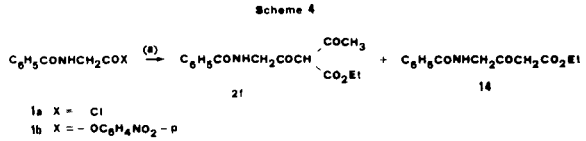


(a) One mole of **1a** or **1b**, 2 moles of *t*-BuOK/*t*-BuOH and 3 moles of $CH_2(CO_2R)_2$ at room temperature for 3 hours. (b) One mole of **1a**, **1b**, **2c** or **2d**, 2 moles of *t*-BuOK/*t*-BuOH and 3 moles of $CH_2(CO_2R)_2$ at room temperature for 12 hours. (c) One mole of **2c** or **2d** and 2 moles of *t*-BuOK/*t*-BuOH at room temperature for 12 hours. (d) Refluxing with two equivalents of NaOMe/MeOH. (e) Refluxing with two equivalents of NaOEt/EtOH-$C_6H_6$.

It is however noteworthy that reaction of **2c** and **2d** with sodium ethoxide in ethanol-benzene (or with an aqueous alkaline solution, see above) results in the formation of the corresponding α-carbalkoxytetramic acids, **3b** and **3c** respectively, through the deacylation-intramolecular condensation reaction.

The reaction of hippuryl chloride (**1a**) or its *p*-nitrophenyl ester (**1b**) with ethyl acetoacetate (Scheme 2) should be limited to 1 hour and should not anyway exceed a reaction time of 3 hours at room temperature, in order to avoid a decomposition of the hippurylacetoacetate formed. Even for a reaction time of 3 hours between **1a** and ethyl acetoacetate, two compounds could be isolated by column chromatography: the *C*-acylation product **2f** in 34% yield and a new compound, in 6% yield, which was characterized (see Experimental) as ethyl hippurylacetate (**14**) (Scheme 4). The crude reaction product from the chloride **1a** with ethyl acetoacetate was then shown, from

Scheme 4




(a) One mole of **1a** or **1b**, 2 moles of $NaH/C_6H_6$ and 3 moles of $CH_3COCH_2CO_2Et$ at room temperature for 3 hours.

its pmr spectrum, to be a mixture of **2f** and **14** in a proportion of about 6:1 for a reaction time of 3 hours and about 1:1 for a reaction time of 18 hours. Compound **14** should arise from a decomposition reaction of the *C*-acylation compound **2f**, similar to the base-induced decomposition of α-acyl derivatives of acetoacetic esters (31). It should however be noted that the reaction of the chloride **1a** or the active ester **1b** with methyl acetoacetate proceeded without decomposition, even for a prolonged reaction time.

## Conclusion.

The successive reactions **1** → **2** → **3** of Scheme 2 constitute eventually a method of synthesis of α-Y-substituted tetramic acids starting with suitable derivatives of hippuric acid. The foregoing results indicate that the benzoylaminoacetyl derivatives of active methylene compounds react with bases in a manner analogous to the corresponding *S*-acetylthioacetyl and acetoxyacetyl derivatives (Scheme 1, B, C and D). All these reactions seem to proceed by a similar concerted deacylation — intramolecular condensation step such as **8**. Further research concerning the cyclization of acetylaminoacetyl derivatives (Scheme 1, D; R' = $CH_3$) is currently in progress in our laboratory.

## EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. The ir spectra were obtained with a Beckman IR 5A or a Perkin Elmer 267 spectrometer. Pmr spectra were recorded on a Varian EM-360 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 ether and the spots were observed by exposure to iodine vapors. For column chromatography, silica gel 60 (63-200 mesh) in benzene was used, approximately 30 g of silica gel for 1 g of product. 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 alcoholic solution of the product. Elemental analyses were obtained from the microanalytical laboratory of CNRS (France).

### Hippuryl Chloride (**1a**).

This compound was prepared from the reaction of hippuric acid with acetyl chloride and phosphorus pentachloride (32) and was used immediately after its preparation for the *C*-acylation reactions. The following procedure was found to give a product of satisfactory purity.

In a 250 ml conical flask are added successively acetyl chloride (50 g, 0.64 mole), phosphorus pentachloride (6.5 g, 0.031 mole) and hippuric acid (5 g, 0.028 mole). The flask is then stoppered and the mixture shaken vigorously for 0.5 hour. The stopper should be withdrawn from time to time, in order to let escape the hydrogen chloride evolved. The initially insoluble hippuric acid is converted first to a pulpy mass and then a yellowish precipitate is formed. This is rapidly filtered, washed with petroleum ether and dried under vacuum over phosphorus pentoxide for 0.5 hour. The purity of the product (4.1 g, 75%) can be judged from its mp. The melting should begin at about 105-110° and should be complete with decomposition up to 125°, lit (32) mp 125° dec. If the melting is not complete at 125°, the product contains a considerable amount of hippuric acid and is unsuitable for further reaction. This procedure was used successfully for up to 10 g of hippuric acid.

### Hippuric Acid *p*-Nitrophenyl Ester (**1b**).

This ester was prepared by the method (33) of direct esterification of *N*-acylamino acids with *p*-nitrophenol in the presence of DCC in methylene chloride. A mixture of 0.03 mole of hippuric acid, 15 ml of methylene chloride and 0.03 mole of *p*-nitrophenol was stirred and warmed to 50-60°, while a solution of 0.03 mole of DCC in 15 ml of methylene chloride was added dropwise. During the addition, which requires about 45 minutes, the temperature of the mixture was maintained at 50-60°. The initially insoluble amino acid dissolves when part of the DCC solution has been added, then dicyclohexyl urea begins to precipitate while the supernatant liquid develops a yellow colour. After the addition of the DCC solution, the mixture was still stirred and warmed for 15 minutes. After cooling the mixture for 1 hour, the precipitated dicyclohexyl urea was filtered, washed with ethyl acetate and the combined filtrates were concentrated under vacuum. The residual solid of crude *p*-nitrophenyl ester **1b** was treated with ether, which removes the *p*-nitrophenol, filtered and washed again with ether. The removal of the *p*-nitrophenol and the purity of the ester **1b** were controlled by tlc. A part of this ester, which is not very soluble in methylene chloride and ethyl acetate, was recovered from the precipitate of dicyclohexyl urea by treatment with warm ethanol. The ester **1b** was thus obtained in 59% yield as a solid mp 158-161°, which was used for the *C*-acylation reactions. Further recrystallizations from ethanol gave a product mp 164.5-166.5°, lit mp 168-169° (34) and 170-173° (35); ir (nujol): strong sharp bands at 3311 (amide -NH-), 1739 (ester carbonyl), 1645 (amide carbonyl) and a strong broad band at 1543 $cm^{-1}$ (amide II); pmr (deuteriochloroform and trifluroacetic acid): 4.70 (d, J = 5 cps, 2H, $-CH_2COO-$) and 7.28-8.62 ppm (m, 10 H, aromatic protons and -CONH-).

### General Procedure for the *C*-Acylation Reaction **1** → **2**.

a) Using Potassium *t*-Butoxide as the Base.

Potassium *t*-butoxide (0.01 mole) is dissolved in 20 ml of *t*-butyl alcohol by stirring at room temperature for about 15 minutes, 0.015 mole of active methylene compound $Y-CH_2-CO_2R$ is added dropwise (a thick white slurry is formed for Y = -CN and $-CO_2R$) and the mixture is stirred for 1 hour. Compound **1** (0.005 mole), acid chloride **1a** (method A) or *p*-nitrophenyl ester **1b** (method B), is then added and the mixture stirred at room temperature for 2-3 hours. Water is added (about 100 ml), the solution is extracted with ether and the aqueous layer is cooled with ice-water and acidified with 10% hydrochloric acid. The ethereal layer is extracted twice with water and the aqueous layers are also acidified. From the acid aqueous solutions the *C*-acylation compound **2** separates either as a solid which is filtered or as an oil which is extracted with chloroform.

b) Using Sodium Hydride as the Base.

In 0.01 mole of sodium hydride (55-60% sodium hydride in oil) in 15 ml of anhydrous benzene, 0.015 mole of the active methylene compound $Y-CH_2-CO_2R$ is added dropwise, when a thick white slurry is formed, and the mixture is stirred for 1 hour. Compound **1** (0.005 mole), acid chloride **1a** (method C) or *p*-nitrophenyl ester **1b** (method D), is then added and the mixture stirred at room temperature for 2-3 hours. After addition of 25 ml of water, the benzene layer is separated and extracted twice with water and the aqueous layers are acidified with 10% hydrochloric acid. The *C*-acylation compound **2** separates either as a solid which is filtered or as an oil which is extracted with chloroform.

Physical characteristics of all *C*-acylation compounds **2** are reported in Table 3.

Table 3

Physical Data of the Benzoylaminoacetyl Derivatives **2**

| Compound (a) | Method (b) | Crude product (c) mp (yield) | Analytical sample mp (recrystallization solvent) | Molecular formula | Analytical data (d) C | H | N |
|---|---|---|---|---|---|---|---|
| **2a** | A | 139-144° (66%) | 146-147° | $C_{13}H_{12}N_2O_4$ | 60.08 | 4.72 | 10.92 |
| | D | 135-141° (52%) | (chloroform-petroleum ether | | (59.99) | (4.65) | (10.77) |
| **2b** | A | 135-137° (57%) (e) | 136-138° (f) | | | | |
| | C | 131-135° (72%) (e) | (chloroform-petroleum ether) | | | | |
| | D | 129-134° (47%) | | | | | |
| **2c** | A | 84-87° (57%) (g) | 88.5-90.5° | $C_{14}H_{15}NO_6$ | 57.26 | 5.15 | 4.93 |
| | B | 85-87° (43%) (h) | (benzene-petroleum ether) | | (57.33) | (5.16) | (4.78) |
| **2d** | A | 77-79° (64%) (g) | 80.5-82.5° (i) | $C_{16}H_{19}NO_6$ | 59.99 | 5.85 | 4.48 |
| | B | 78-81° (45%) (h) | (benzene-petroleum ether) | | (59.80) | (5.96) | (4.36) |
| **2e** | B | 79-81° (54%) (j) | 78-79.5° | $C_{14}H_{15}NO_5$ | 60.64 | 5.45 | 5.05 |
| | C | 77-79° (48%) | (chloroform-petroleum ether) | | (60.76) | (5.42) | (5.04) |
| **2f** | B, C or D | oily product (k) | | | | | |

(a) See Scheme 2. (b) See Experimental: method A, acid chloride **1a** and *t*-BuOK; method B, ester **1b** and *t*-BuOK; method C, acid chloride **1a** and NaH; method D, ester **1b** and NaH. (c) Product used for the cyclization reaction **2** → **3**. (d) Values in parentheses refer to calculated values. (e) The solid obtained from the reaction was dissolved in warm chloroform, in order to eliminate any insoluble hippuric acid present, and was then precipitated by addition of petroleum ether. (f) Lit (21) mp 139°. (g) The oily product obtained from the reaction crystallized on cooling; this was treated with warm benzene, in order to eliminate any insoluble hippuric acid and/or compound **11**, and was then precipitated by addition of petroleum ether. (h) The oily product obtained from the reaction contained a large amount of *p*-nitrophenol and was purified by column chromatography; the solid product which was eluted with chloroform still contained some *p*-nitrophenol (tlc and pmr spectrum). (i) Lit (21) mp 85°. (j) Some *p*-nitrophenol is present (tlc and pmr spectrum). (k) See Experimental.

The crude compounds **2a-2e** were found to be sufficiently pure (tlc and pmr spectra) and were used as such for the cyclization reaction **2** → **3**. The pmr and ir spectra of their analytically pure samples are reported in Tables 1 and 2 respectively. Compound **2f** was isolated as a complex oily mixture containing ethyl acetoacetate, *p*-nitrophenol (methods B and D) and ethyl hippurylacetate (**14**). The purification of compound **2f** by column chromatography and the isolation of compound **14** are described below.

Ethyl Hippurylacetoacetate (**2f**) and Ethyl Hippurylacetate (**14**).

Following method C, the oily product obtained after acidification was shown in tlc to be a complex mixture. This was extracted repeatedly with ether and the ether extract was dried and concentrated under vacuum. Three g of an oily product were thus obtained from 4 g of acid chloride **1a** and were submitted to column chromatography. Elution with benzene gave initially a mixture of ethyl acetoacetate and compound **2f**. Elution with benzene-chloroform 1:1 gave 1.96 g (34%) of an oily product which was considered to be sufficiently pure compound **2f**, since tlc and its pmr spectrum (Table 1) showed it to contain only a small proportion of ethyl acetoacetate. This product was used for the cyclization reaction to α-acetyltetramic acid (**3d**) (see below).

Further elution with chloroform gave 0.3 g (6%) of a product mp 92-95°, which was characterized as ethyl hippurylacetate (**14**). The product did not give any colour with ferric chloride. An analytical sample mp 94-96°, was obtained by recrystallization from chloroform-petroleum ether; ir (nujol): strong sharp bands at 3240 (amide -NH-), 1725 (ester and ketone carbonyl), 1630 (amide carbonyl) and 1525 $cm^{-1}$ (amide II); pmr (deuteriochloroform): 1.25 (t, J = 7 cps, 3H, $-CH_2CH_3$), 3.55 (s, 2H, $-COCH_2CO-$), 4.22 (q, J = 7 cps, 2H, $-CH_2CH_3$), 4.46 (d, J = 5 cps, 2H, $-NHCH_2CO-$), 7.11 (m, 1H, -CONH-) and 7.41-7.97 ppm (m, 5H, aromatic protons).

*Anal.* Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.60; H, 6.15; N, 5.80.

Following method D, after acidification and extraction with ether, 3.74 g of an oily product were obtained from 3 g of ester **1b**. Column chromatography of this product gave initially a mixture of *p*-nitrophenol and ethyl acetoacetate (elution with benzene) and then (elution with benzene-chloroform 1:1) 52% of compound **2f** as an oily product containing again (pmr spectrum) only a small proportion of ethyl acetoacetate.

α-Cyanotetramic Acid (**3a**).

One g (3.7 mmoles) of compound **2b** 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 12 ml of methanol). The solution was refluxed for 10 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 **2b**, and ether, to eliminate the benzoic ester. The product was then dissolved in warm ethanol, to eliminate sodium chloride, filtered and the solvent evaporated to give 0.21 g (46%) of compound **3a**, mp 210° dec. An analytical sample was obtained on recrystallization from water, mp 217-219°, lit (36) initial melting with dec at 210°, complete melting at 220-221°; ir (nujol): 3165 m, br, 2220 m, 1720 w, 1680 s and 1640-1620 s, br $cm^{-1}$; pmr (DMSO-$d_6$); 3.96 (s, 2H, ring $-CH_2-$) and 9.24 ppm (br, 2H, -NH- and -OH).

*Anal.* Calcd. for $C_5H_4N_2O_2$: C, 48.39; H, 3.25; N, 22.58. Found: C, 48.42; H, 3.39; N, 22.14.

Following the same procedure described above, 260 mg of compound **2a** yielded 60 mg (48%) of compound **3a**, mp 214-216° dec.

Compound **3a** was also obtained by treatment of **2b** in an aqueous alkaline solution as follows. One g of **2b** was added to a solution of 3 g of sodium carbonate in 40 ml of water. In the turbid solution was added a

solution of 4.5 g of sodium hydroxide in 10 ml of water. The precipitate which formed initially was redissolved after 6 hours. The mixture was stirred at room temperature for 3 days, then cooled and acidified with concentrated hydrochloric acid. The solution was concentrated under vacuum and the solid residue was treated successively with ether, to eliminate benzoic acid, and chloroform, to eliminate any starting compound **2b**. The product was then dissolved in warm ethanol, filtered and the solvent evaporated to give 0.28 g (62%) of compound **3a**, mp 212-216° dec.

α-Carbomethoxytetramic Acid (**3b**).

Compound **2c** (0.9 g, 3 mmoles) was dissolved in 20 ml of warm benzene and added to a solution of sodium ethoxide in ethanol (prepared from 0.14 g or 0.006 g-atom of sodium in 10 ml of absolute ethanol). The mixture, in which a yellowish precipitate was formed, was refluxed for 5 hours and let stand overnight. The precipitate was dissolved by addition of water and the solution acidified with 10% hydrochloric acid. The aqueous layer was cooled for some time and the white crystals formed were filtered, washed with water and dried to give 320 mg (66%) of **3b**, mp >270°, lit mp ≅ 360° (8), >300° (10) and >360° (12). An analytical sample was obtained by dissolution in a solution of sodium bicarbonate and reprecipitation with dilute hydrochloric acid; ir (nujol): 3360 w, 3278 m, sh, 1710 m, 1672 s, br and 1620 s, br $cm^{-1}$; pmr (trifluoroacetic acid): 4.02 (s, 3H, $-COOCH_3$) and 4.42 ppm (s, 2H, ring $-CH_2-$).

*Anal.* Calcd. for $C_6H_7NO_4$: C, 45.86; H, 4.49; N, 8.91. Found: C, 45.72; H, 4.41; N, 8.93.

α-Carbethoxytetramic Acid (**3c**).

Following the procedure described for **3b**, compound **3c** was prepared from **2d** in 34% yield, mp at about 120°, followed by resolidification and no further melting up to 270°, lit (10) transient melting at *ca.* 140° followed by resolidification and no further melting to 300°; ir (nujol): 3448 m, 3145 s, sh, 1703 s, br, 1660 s, br and 1626 m $cm^{-1}$; pmr (trifluoroacetic acid): 1.48 (t, J = 7 cps, 3H, $-COOCH_2CH_3$), 4.46 (s, ring $-CH_2-$) and 4.58 ppm (q, J = 7 cps, $-COOCH_2CH_3$); the signals at 4.46 and 4.58 ppm integrate for 4 protons.

*Anal.* Calcd. for $C_7H_9NO_4$: C, 46.67; H, 5.59; N, 7.78. Found: C, 46.56; H, 5.51; N, 8.02.

Compound **3c** was also obtained by treatment of **2d** in an aqueous alkaline solution, by the procedure described for compound **3a**. Acidification of the reaction mixture gave a precipitate which was filtered, dried and treated with ether, in order to eliminate benzoic acid. Compound **3c** was thus obtained in 68% yield.

α-Acetyltetramic Acid (**3d**).

Compound **2f** (0.58 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 yellow precipitate was formed, was refluxed for 3 hours and let stand overnight. The precipitate was dissolved by addition of water, the benzene layer was washed twice by 3 ml of water and the aqueous layers were acidified with concentrated sulfuric acid. The acid solution was repeatedly extracted with ether after addition of sodium chloride and the solvent removed under vacuum. The oily residue crystallized by addition of petroleum ether and was recrystallized from ethyl acetate-petroleum ether to give 0.13 g (46%) of a product mp 149-151°, lit mp 155° (3), 148-150° (4), 155° (6) and 154-155° (37); ir (nujol): 3280 w, 3125 m, br, 1710 s, sh, 1660 s, br and 1612 s, br $cm^{-1}$; pmr (DMSO-$d_6$): 2.40 (s, 3H, $-COCH_3$), 3.78 (s, 2H, ring $-CH_2-$), 8.50 (br m, 1H, -NH-) and 13.30 ppm (s, 1H, -OH).

The procedure described above was used for the cyclization of compound **2e**. The aqueous layers were acidified with 10% hydrochloric acid, the acid solution was extracted first with chloroform and then with ether, and the solvents evaporated under vacuum. The solid residue was treated with a small quantity of ether to give compound **3d**, mp 148-152°, in 63% yield.

Compound **3d** was also obtained from hippuryl chloride (**1a**), without isolating the intermediate *C*-acylation product, by the following procedure.

Sodium (0.46 g, 0.02 g-atom) was dispersed in 30 ml of anhydrous toluene under vigorous agitation and heating. The dispersion was then cooled in ice and 3.9 g (0.03 mole) of ethyl acetoacetate were added dropwise, when a thick slurry was formed. When all of the sodium had reacted, 1.98 g (0.01 mole) of hippuryl chloride (**1a**) partially dissolved in anhydrous toluene was added and the mixture was stirred at room temperature overnight. The thick yellow suspension was acidified with 15 ml of 10% hydrochloric acid, the initially formed precipitate was dissolved by agitation and a small quantity of thin suspended material was filtered. The two layers were separated and the organic layer was extracted repeatedly with about 80 ml of a 10% sodium carbonate solution, until the alkaline extract was no more coloured yellow. Eight g of sodium hydroxide in 30 ml of water were added to the carbonate extract and the mixture was stirred at room temperature for 3 days. The alkaline solution was acidified with concentrated hydrochloric acid and the acid solution was repeatedly extracted with ether after adding sodium chloride. The solvent was removed under vacuum and the solid residue was treated with a small quantity of ether in order to eliminate any benzoic acid present. Compound **3d** (0.58 g, 41%) was thus obtained, mp 150-154°.

*N*-Benzoyl-α-benzoylaminotetramic Acid (**11**).

Hippuryl chloride (**1a**) reacted with methyl or ethyl malonate according to the general procedure (method A) described for the *C*-acylation reaction **1** → **2**, except that the mixture was stirred, after addition of the acid chloride, at room temperature for 12 hours. Acidification gave a solid, in 54% and 67% yield from methyl and ethyl malonate respectively, mp 122°, after recrystallization from ethanol. For the hydrated form of **11** (+ ½ $H_2O$) were reported mp 108-110° (28), 116° (29) and 115-123° (30). After drying, the product had mp 138°, lit mp 137-138° (28) and 140-141° (30). The spectroscopic (ir and pmr) data of this compound were found to be identical to those already published (30).

Compound **11** was also obtained from methyl hippurylmalonate (**2c**) under the conditions of the *C*-acylation reaction **1** → **2**. For example, stirring a mixture of **2c** (1 mmole), methyl malonate (2 mmoles) and potassium *t*-butoxide (2 mmoles) in 10 ml of *t*-butyl alcohol at room temperature for 24 hours, resulted in the isolation of compound **11** in almost quantitative yield. Under the same conditions but without adding methyl malonate, compound **11** was isolated in 64% yield.

The formation of a product mp 116°, along with ethyl hippurylmalonate (**2d**), from the reaction of hippuryl chloride (**1a**) with ethyl sodiomalonate, had been reported (21). This product, which had been characterized as *N,N'*-dibenzoyldiketopiperazine, is obviously the hydrated form of compound **11**.

α-Benzoylaminotetramic Acid (**13**).

Methyl hippurylmalonate (**2c**) (0.9 g, 3 mmoles) was dissolved in 20 ml of methanol and added to a solution of sodium methoxide in methanol (prepared from 0.14 g or 0.006 g-atom of sodium in 20 ml of methanol). The mixture was refluxed for 4 hours and let stand overnight. The alcohol was eliminated under vacuum, 10 ml of water were added to the residue and the solution was acidified with 10% hydrochloric acid. Compound **13** (560 mg, 83%) was obtained, mp 186-190°. Recrystallization from ethanol gave a product mp 203-205°, lit mp 205° (29) and 200.5° (38); pmr (deuteriochloroform + DMSO-$d_6$): 3.90 (s, 2H, ring $-CH_2-$), 7.35-8.15 (m, 6H, aromatic protons and $-CH_2NHCO-$), 8.85 (almost a s, 1H, $-NHCOC_6H_5$) and 11.80 ppm (s, 1H, enolic -OH).

Compound **13** was also obtained from a similar treatment of either ethyl hippurylmalonate (**2d**) or *N*-benzoyl-α-benzoylaminotetramic acid (**11**) in 68% and 51% yield respectively.

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## REFERENCES AND NOTES

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