Amidines. IV. Hydrolysis of N^1-Acyl Derivatives of N^1,N^2-Diarylamidine in Carboxylate Buffer Solution

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In the hydrolysis of N^1-benzoyl-N^1,N^2-diphenylacetamidine (1) in carboxylate buffer solutions, nucleophilic attack of the catalytic acid was proved to take place at the amide carbonyl carbon (pathway d) and presumably also at the amidine central carbon (pathway e) in parallel to the normal hydrolysis processes. Mixed acid anhydride and N^1,N^2-diphenylacetamidine were formed by pathway d, and the former reacted with aniline formed by further hydrolysis of the latter to give two *N*-acylanilines. In parallel with this process, the mixed anhydride reacts with water to give two carboxylic acids. In this case, carboxylic acid acts as a nucleophilic catalyst.

The reaction of 1 and *p*-methoxybenzoic acid under anhydrous conditions gave products derived from the attack of *p*-methoxybenzoate ion at both amide carbonyl and amidine central carbons.

Hydrolysis of N^1-benzoyl-N^1,N^2-diphenylformamidine (7) in acetate buffer solution proceeded mainly through the ordinary hydrolysis pathway. Formation of a small amount of acetanilide implies that the reaction proceeds through pathway d or e to a small extent.

In hydrolysis of N^1-tosyl-N^1,N^2-di(*p*-methylphenyl)acetamidine (6b) in glycolate buffer solution, a small amount of *N*-(acetoxyacetyl)-*p*-toluidine was formed together with the ordinary hydrolysis products. This implies that the reaction proceeds through pathway e to a small extent.

Keywords *N*-benzoylacetamidine; *N*-benzoylformamidine; *N*-tosylacetamidine; hydrolysis; nucleophilic catalyst; reaction pathway; structure–reactivity relationship

In a previous paper[1] we reported the hydrolysis of N^1-acyl-N^1,N^2-diarylamidines under acidic and basic conditions. Attack of water was proved to take place exclusively at the amidine central carbon and the reaction proceeded through pathways a and b (Chart 1) under acidic conditions, while the attack of hydroxide ion takes place at the amide carbonyl carbon to give diarylamidine and carboxylic acid under alkaline conditions (pathway c, Chart 1) except for the case of N^1-(*p*-chlorobenzoyl)-N^1,N^2-di(*p*-nitrophenyl)formamidine.

In this paper we will report the hydrolysis of N^1-benzoyl-N^1,N^2-diphenylacetamidine (**1**) in carboxylate buffer solutions. Nucleophilic attack of the carboxylate ion was proved to take place at both the amidine central carbon (pathway e) and amide carbonyl carbon (pathway d) in parallel with the hydrolysis process, pathways a and b.

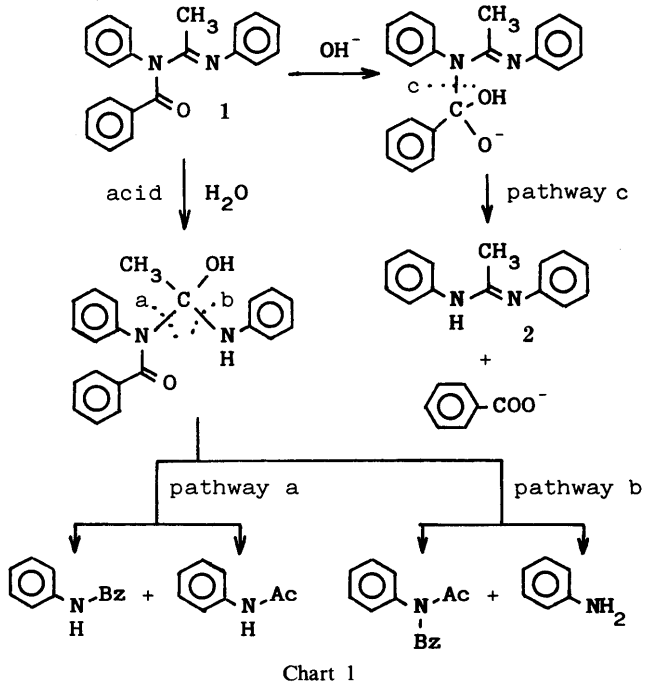


Chart 1

Hydrolysis of N^1-benzoyl-N^1,N^2-diphenylformamidine (**7**) in acetate buffer solution proceeded mainly through pathways a and b. Formation of a small amount of acetanilide implies that the reaction proceeds with incorporation of the catalytic acid to a small extent.

Hydrolysis of N^1-Benzoyl-N^1,N^2-diphenylacetamidine (1) in Carboxylate Buffer Solutions Benzanilide (6%), acetanilide (36%), N^1,N^2-diphenylacetamidine (**2**) (37%), aniline (10%) and benzoic acid (57%) were obtained when **1** was heated under reflux for 3.5 h in 80% aqueous dioxane solution containing equimolar amounts of acetic acid and sodium acetate. The product ratio, benzanilide : acetanilide, was also determined to be 1 : 4 by high-performance liquid chromatography (HPLC). The result that only a rather small amount of benzanilide was formed shows that the contribution of pathway a to the whole reaction sequence was small. The contribution of pathway b should also be insignificant because most *N*-benzoyl-*N*-acetylaniline was recovered after treatment under the same conditions: the ratio of benzanilide, acetanilide formed and recovered *N*-benzoyl-*N*-acetylaniline was evaluated to be 7 : 11 : 81 by HPLC. In benzoate buffer solution, the ratio of benzanilide to acetanilide formed in the hydrolysis of **1** increased to 3 : 7. These results imply that the carboxylic acid used as a catalyst would be incorporated into the products. The incorporation of the catalytic acid was confirmed by the following ^{1}H nuclear magnetic resonance (^{1}H-NMR) experiments. When an 80% aqueous dioxane solution of **1** was refluxed for 3.5 h in the presence of equimolar amounts of trideuterioacetic acid and sodium trideuterioacetate, 33% of trideuterioacetanilide was incorporated in the fraction isolated as acetanilide from the reaction mixture. When an 80% aqueous dioxane solution of **2** was refluxed for 3.5 h

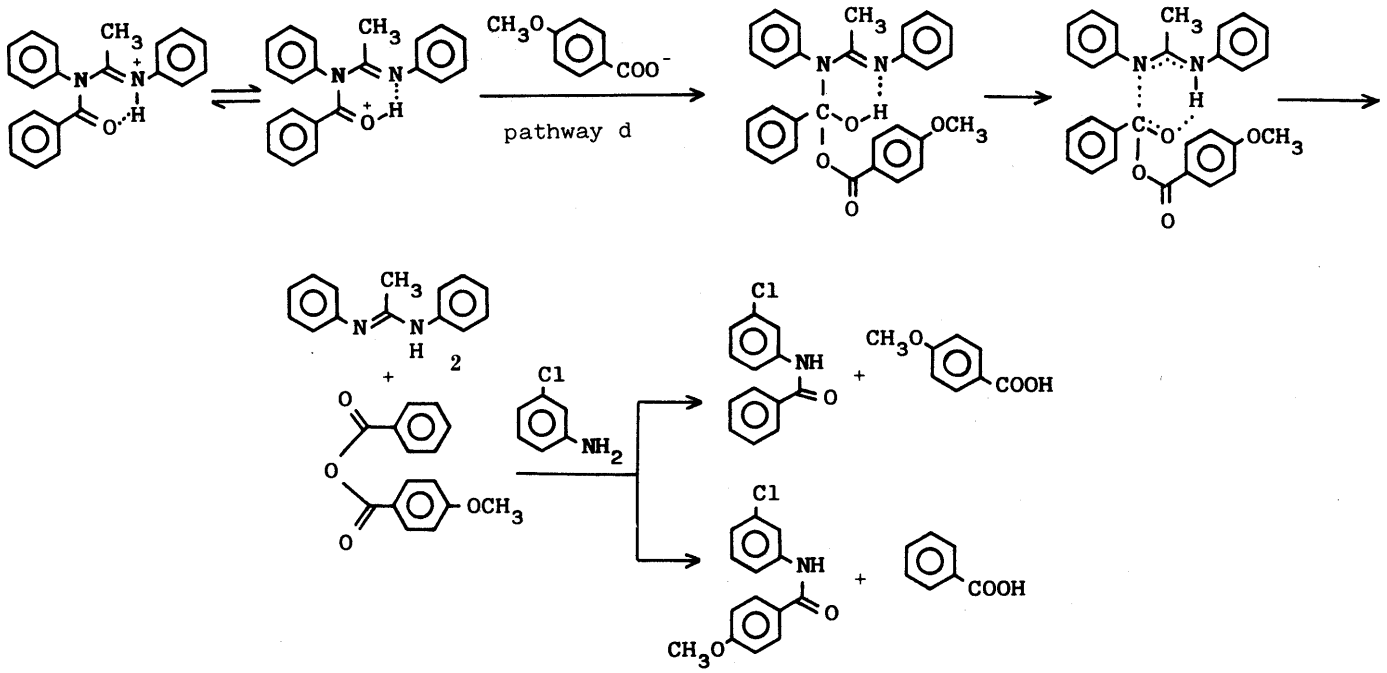


Chart 2

in the presence of equimolar amounts of trideuterioacetic acid and sodium trideuterioacetate, acetanilide, aniline and about a half of the starting material were isolated from the reaction mixture. Acetanilide thus obtained was proved not to contain any trideuterioacetanilide. Furthermore, acetanilide obtained by hydrolysis of *N*-benzoyl-*N*-acetylaniline in trideuterioacetate buffer solution did not contain deuterated acetanilide. The results show that trideuterioacetanilide obtained by hydrolysis of **1** in trideuterioacetate buffer solution should not be derived from the hydrolysis products by pathways a and b.

The interaction of **1** and carboxylic acid was examined under anhydrous conditions to elucidate other possible pathways of hydrolysis of **1**. A dioxane solution of an equimolar mixture of **1** and *p*-methoxybenzoic acid was refluxed for 2 h, and allowed to cool to room temperature. Two equivalents of *m*-chloroaniline was added to the reaction mixture, and the mixture was kept for 1 d at room temperature. Benzanilide (12%), acetanilide (33%), *N*-(*p*-methoxybenzoyl)aniline (15%), *N*-benzoyl-*m*-chloroaniline (13%), *N*-acetyl-*m*-chloroaniline (5%), *N*-(*p*-methoxybenzoyl)-*m*-chloroaniline (13%) and **2** (13%) were obtained together with a mixture of benzoic acid and *p*-methoxybenzoic acid (4:6 by ^{1}H-NMR integration) from the reaction mixture. The formation of *N*-benzoyl-*m*-chloroaniline and *N*-(*p*-methoxybenzoyl)-*m*-chloroaniline implies the formation of benzoic *p*-methoxybenzoic anhydride in the reaction of **1** and *p*-methoxybenzoic acid.

The pathway of mixed anhydride formation is probably as shown in Chart 2. Immonium cation enhances the electrophilicity of the amide carbonyl carbon by chelation, promoting nucleophilic attack of the carboxylate ion, and the electron-rich system of amidine produces a driving force to leave the tetrahedral intermediate so forming the carboxylic anhydride. Bender and Neveu[2] reported an instance of nucleophilic attack of carboxylate ion at an ester carbonyl carbon, *i.e.*, hydrolysis of 2,4-dinitrophenyl benzoate by acetate-^{18}O buffer gave benzoic acid-^{18}O.

Assuming that the nucleophilic attack of carboxylate ion at the amide carbonyl carbon and subsequent elimination of mixed anhydride, pathway d, takes place in the hydrolysis of **1** in buffer solution, formation of anilides of carboxylic acids could be explained as follows, *i.e.*, the mixed anhydride would react with aniline formed by hydrolysis of **2** which is produced from **1** by pathway d.

Formation of benzanilide, acetanilide, *N*-(*p*-methoxybenzoyl)aniline, *N*-acetyl-*m*-chloroaniline and *N*-(*p*-methoxybenzoyl)-*m*-chloroaniline in the reaction of **1**, *p*-methoxybenzoic acid and *m*-chloroaniline, however, can not be explained even by pathway d. This phenomenon can be explained on the assumption that nucleophilic attack of carboxylate ion at the amidine central carbon and the subsequent elimination of benzanilide to give *N*-phenylacetimidic *p*-methoxybenzoic anhydride (**5**) from the tetrahedral intermediate, pathway e, takes place in the reaction of **1** and *p*-methoxybenzoic acid (Chart 3). 1,3-*O*,*N*-Acyl migration of **5** would afford *N*-(*p*-methoxybenzoyl)-*N*-acetylaniline, and the latter reacts with *m*-chloroaniline to give *N*-(*p*-methoxybenzoyl)aniline, *N*-acetyl-*m*-chloroaniline, acetanilide and *N*-(*p*-methoxybenzoyl)-*m*-chloroaniline. Curtin and Miller[3] reported 1,3-*O*,*N*-acyl migration of *N*-(2,4-dinitrophenyl)benzimidic benzoic anhydride to give *N*,*N*-dibenzoyl-2,4-dinitroaniline.

Hydrolysis of **1** in acetate buffer solution is presumed to proceed through pathway d and perhaps pathway e in parallel with pathways a and b (Charts 4 and 1). Pathways a and b might be rather unimportant in the whole hydrolysis process in view of the relatively small amount of benzanilide formed. Probably pathway d is the main course of hydrolysis of **1** in buffer solution. Formation of **2**, large amounts of acetanilide and benzoic acid, and 33% incorporation of trideuterioacetic acid used as a catalyst are well explained by pathway d. There is no evidence for the contribution of pathway e to the whole sequence of hydrolysis of **1**. The contribution of pathway e would be insignificant even if it exists, because pathway e would predict

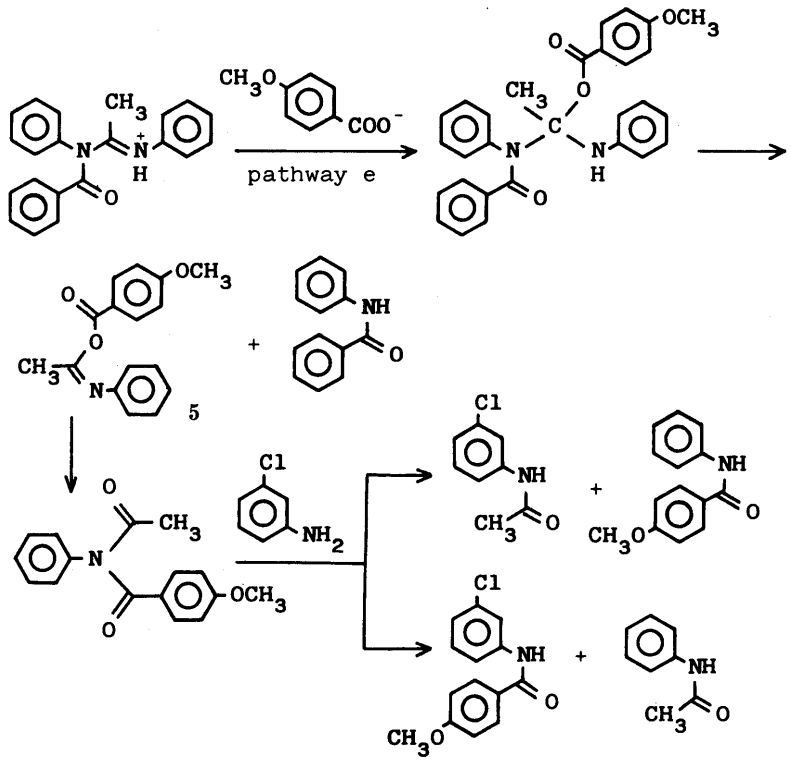


Chart 3

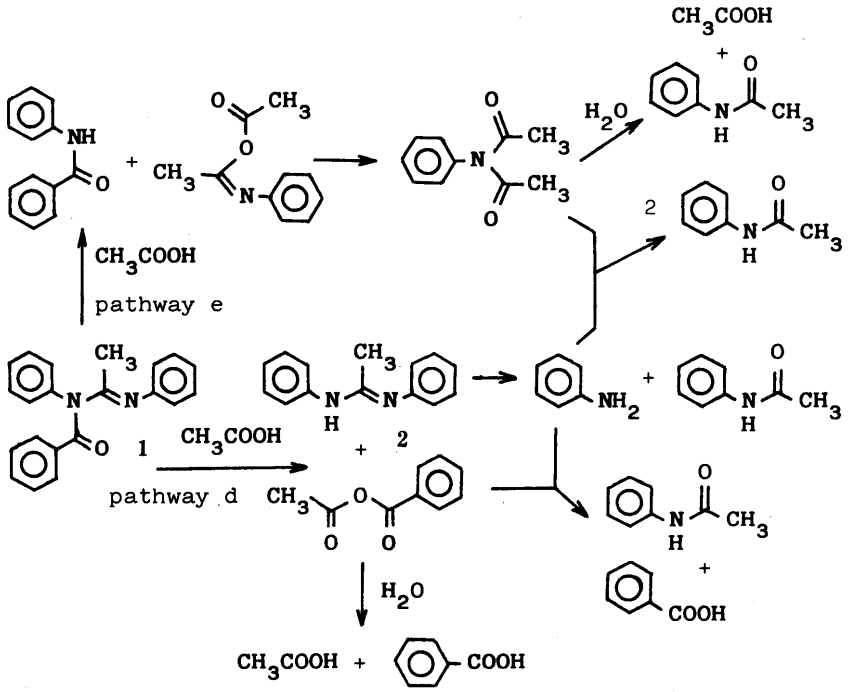


Chart 4

formation of benzanilide and equal amounts of acetanilide and deuterated acetanilide in trideuterioacetate buffer solution. As described in the later part of this report, evidence for pathway e was obtained for the hydrolysis of N^1-tosyl-N^1,N^2-diarylacetamidine (**6**) in buffer solution.

Hydrolysis of N^1-Benzoyl-N^1,N^2-diphenylformamidine (7) in Acetate Buffer Solutions N^1-Benzoyl-N^1,N^2-diphenylformamidines (**7**) were prepared by the reaction of benzoyl chloride and N^1,N^2-diphenylformamidine (**8**). Benzanilide (91%), formanilide (63%), aniline (19%), benzoic acid (4%) and acetanilide (7%) were obtained when **7** was heated under reflux for 4.7 h in an 80% aqueous dioxane solution in the presence of equimolar amounts of acetic acid and sodium acetate. Compound **8** could not be detected in the reaction mixture (Chart 5). Formanilide (69%) and aniline (58%) were formed when an 80% aqueous dioxane solution of **8** was warmed at 40 °C for 6 h in the presence of equimolar amounts of acetic acid and sodium acetate.

Acetanilide could not be detected in the reaction mixture. Most of the starting material (86%) was recovered when formanilide was treated under the same conditions.

The results show that the hydrolysis of **7** proceeds mainly through pathway a, and incorporation of the catalytic acid into the products (pathway d or e) takes place to a small extent. The absence of **8** in the products is probably because of greater susceptibility of **8** to hydrolysis as compared with that of **2**.[4]

The hydrolysis of N^1-acyl-N^1,N^2-diarylamidine is initiated by nucleophilic attack of water at the central carbon of the conjugate acid of N^1-acyl-N^1,N^2-diarylamidine. An electron-releasing methyl group at the central carbon of **1** enhances the basicity of the substrate so increasing the equilibrium concentration of reactive conjugate acid while decreasing the susceptibility of the central carbon to nucleophilic attack by water. The latter of these opposing effects would play a more important role in the acid hydrolysis of N^1-acyl-N^1,N^2-diarylamidines because the hydrolysis of N^1-acyl-N^1,N^2-diarylformamidine proceeded much faster than that of N^1-acyl-N^1,N^2-diarylacetamidine under acidic conditions.[1] The obstructive effect of the central methyl group against nucleophilic attack by water would be insignificant at the amide carbonyl carbon so that pathway d plays a more important role in the hydrolysis of **1** than that of **7**.

In a previous paper[5] we reported hydrolysis of 1-(*N*-benzoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene, a vinylog of N^1-acyl-N^1,N^2-diarylamidine, in acetate buffer solution. The reaction proceeded much faster than that of **7**, and afforded *β*-(*N*-benzoyl-*p*-methylphenylamino)acrolein and *p*-toluidine (corresponding to pathway b) at the first step. Incorporation of the catalytic acid into products could not be observed probably owing to the difficulty of forming a chelate structure of the conjugate acid of the substrate. It is well known that the acetyl transfer reaction readily takes place between various nucleophiles and acetylimidazole, an acetyl derivative of cyclic amidine. However, we are not aware of any instance of acetyl transfer between acetylimidazole and carboxylic

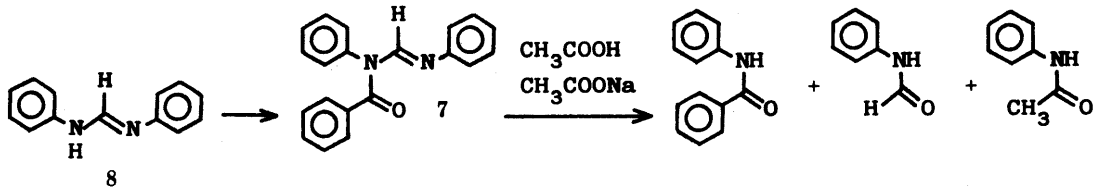
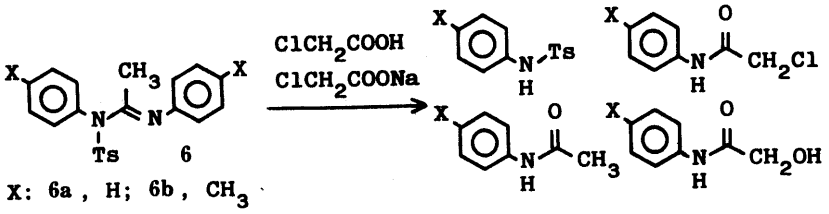
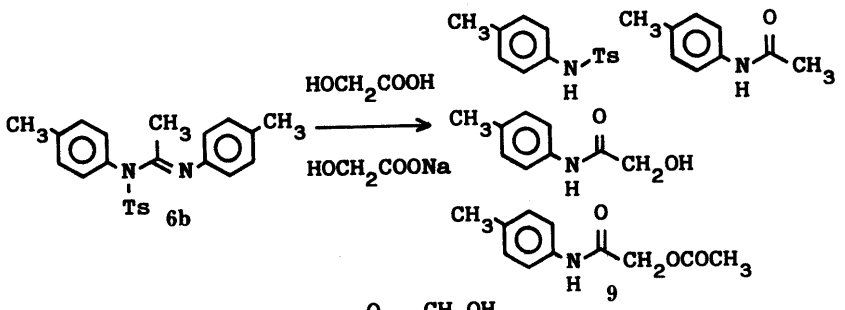


Chart 5





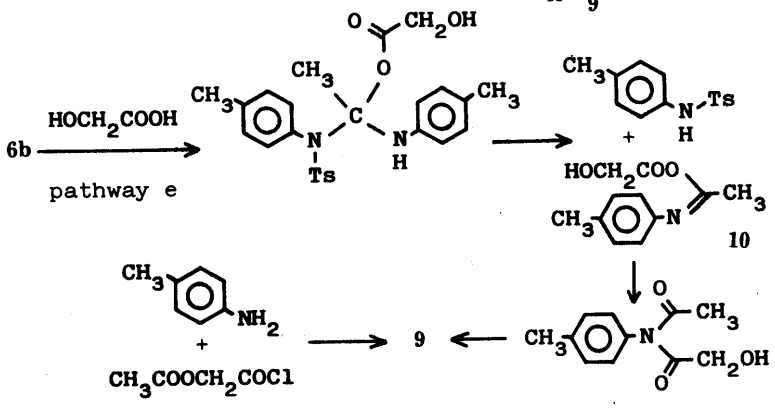


Chart 6

acid, probably also for the above reason.

Hydrolysis of N^1-Tosyl-N^1,N^2-diarylacetamidine (6) in Buffer Solution Hydrolysis of **6** proceeded too slowly to be completed in acetate buffer solution even on prolonged heating of the reaction solution. The reaction was examined under more acidic conditions.

N-Tosylaniline (86%), acetanilide (88%), chloroacetanilide (7%) and hydroxyacetanilide (5%) were obtained when N^1-tosyl-N^1,N^2-diphenylacetamidine (**6a**) was heated under reflux for 27 h in an 80% aqueous dioxane solution in the presence of equimolar amounts of chloroacetic acid and sodium chloroacetate (Chart 6). The results imply that the hydrolysis of **6a** proceeded mainly through pathway a to give *N*-tosylaniline and acetanilide, and probably through pathway e in parallel to a small extent in view of the formation of a small amount of chloroacetanilide. The formation of hydroxyacetanilide is presumably due to the hydrolysis of chloroacetanilide during the reaction. A small amount of *N*-acetyl-*N*-tosylaniline was detected in the reaction mixture when the refluxing time was shortened to 9 h. The fact suggests that the reaction proceeds through pathway b in parallel with pathway a to a small extent.

When an 80% aqueous dioxane solution of N^1-tosyl-N^1,N^2-di(*p*-methylphenyl)acetamidine (**6b**) was refluxed for 19 h in the presence of chloroacetic acid and sodium chloroacetate, *N*-tosyl-*p*-toluidine (92%), *N*-acetyl-*p*-toluidine (91%), *N*-(chloroacetyl)-*p*-toluidine (4%), *N*-(hydroxyacetyl)-*p*-toluidine (5%) and a small amount of a compound melting at 101 °C (**9**) were obtained. The results of elemental analysis of **9** were consistent with the values required for the molecular formula $C_{11}H_{13}NO_3$ and the mass spectrum (MS) of **9** showed a peak at *m/z* 207 (M^+). A small amount of **9** was obtained when **6b** was heated under reflux in a 77% aqueous dioxane solution for 30 h in the presence of equimolar amounts of glycolic acid and sodium glycolate. The structure of **9** was estimated to be *N*-(acetoxyacetyl)-*p*-toluidine on the basis of ^{1}H-NMR and ^{13}C-NMR ($CDCl_3$) evidence, *i.e.*, 5% nuclear Overhauser effect (NOE) was observed on the signal at 7.40 ppm (2H, d, *o*-position) on gated irradiation of the signal at 7.97 ppm (1H, NH, disappeared on addition of deuterium oxide) and the spin–spin coupling (3 Hz) between the NH signal and ^{13}C signal at 120.5 ppm (*o*-position) was proved to exist by low-power selective proton decoupling. The structure of **9** was further ascertained by the identity of the sample with that prepared by the reaction of *p*-toluidine and acetoxyacetyl chloride[6] (Chart 6).

The sequence of the formation of **9** is probably as follows: attack of glycolate ion at the amidine central carbon of **6b** followed by elimination of the *N*-tosyl-*p*-toluidino group from the tetrahedral intermediate affords *N*-(*p*-methylphenyl)acetimidic glycolic anhydride (**10**), then 1,3-*O*,*N*-acyl migration of the latter gives *N*-acetyl-*N*-(hydroxyacetyl)-*p*-toluidine (pathway e), and **9** is formed by intramolecular acylation of the last compound (Chart 6). Formation of **9** provides a proof of the existence of pathway e in the hydrolysis of **6** in buffer solutions.

Experimental

All melting points are uncorrected. ^{1}H-NMR spectra were recorded on JEOL PMX 60 and JEOL GX 400 NMR spectrometers with tetramethylsilane as an internal standard. The following abbreviations are used: singlet (s), doublet (d) and broad (br). Analysis by HPLC was carried out with a Waters liquid chromatograph (ALC/GPC 204A compact type).

The samples of arylamine, *N*-acylarylamine, *N*,*N*-diacylarylamine, *N*-tosylarylamine and *N*-acyl-*N*-tosylarylamine formed in the hydrolysis process were identical with the corresponding authentic samples on the basis of comparison of their infrared (IR) spectra or of both comparison of their IR spectra and mixed melting point measurement. Aniline was identified as its acetyl derivative.

Hydrolysis of 1 in the Presence of AcOH and AcONa, and in the Presence of AcOH-d_3 and AcONa-d_3 A solution of AcOH (0.20 g, 3.3 mmol) and AcONa·3H_2O (0.45 g, 3.3 mmol) in 6 ml of H_2O was added to a solution of **1** (1.05 g, 3.3 mmol) in 24 ml of dioxane. The mixture was refluxed for 3.5 h. After addition of 25 ml of 7% $NaHCO_3$, the solution was concentrated under reduced pressure. The distillate, after being made acidic by addition of HCl, was evaporated to dryness, and the remaining material was treated as usual to give aniline (0.03 g, 10%). Water was added to the residue and the mixture was extracted with CH_2Cl_2. The water layer was treated as usual to give BzOH (0.23 g, 57%). The CH_2Cl_2 layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to preparative TLC (silica gel) with benzene–AcOEt (5 : 1) to give benzanilide (0.04 g, 6%), acetanilide (0.16 g, 36%) and **2** (0.26 g, 37%).

A solution of CD_3COOD (0.43 g, 6.6 mmol) and 3.3 ml of 1 N NaOH and 2.7 ml of H_2O was added to a solution of **1** (1.05 g, 3.3 mmol) in 24 ml of dioxane. The mixture was refluxed for 3.5 h and treated as above to give aniline (0.03 g, 10%), BzOH (0.22 g, 54%), benzanilide (0.04 g, 6%), **2** (0.23 g, 33%) and acetanilide (0.15 g, 33%) which contained 33% $PhNHCOCD_3$ on the basis of ^{1}H-NMR evidence.

The sample for HPLC analysis was prepared as described below. A solution of AcOH (0.1500 g, 2.5 mmol) and AcONa·3H_2O (0.3402 g, 2.5 mmol) in 6.25 ml of H_2O was added to a solution of **1** (0.7855 g, 2.5 mmol) in 25 ml of dioxane. The whole was refluxed for 3.5 h and 15 ml of 7% $NaHCO_3$ was added. The mixture was concentrated under reduced pressure. Water was added to the residue and the mixture was extracted with ether. The water layer was treated as usual to give BzOH (0.2197 g, 72%). The ether layer was dried over Na_2SO_4, and concentrated under reduced pressure. A part of the CH_3CN solution of the residue was subjected to HPLC on a reversed-phase column (μ Bondapak C18) with CH_3CN–0.02 M K_2HPO_4 (1 : 1). The result is described in the main text.

Hydrolysis of 2 in the Presence of AcOH and AcONa, and in the Presence of AcOH-d_3 and AcONa-d_3 A solution of AcOH (0.30 g, 5 mmol) and AcONa·3H_2O (0.68 g, 5 mmol) in 8 ml of H_2O was added to a solution of **2** (1.05 g, 5 mmol) in 32 ml of dioxane. The solution was refluxed for 3.5 h. After addition of 25 ml of 7% $NaHCO_3$, the whole was concentrated under reduced pressure. The distillate, after being made acidic by addition of HCl, was evaporated to dryness, and the remaining material was treated as usual to give aniline (0.16 g, 34%). The residue was extracted with ether, and the ether solution was extracted with 2 N HCl. The deposited HCl salt of **2** was collected, and treated as usual to give **2** (0.53 g, 50%). The ether layer was dried over Na_2SO_4, and concentrated under reduced pressure to give acetanilide (0.18 g, 27%).

A mixture of CD_3COOD (0.64 g, 5 mmol), 5 ml of 1 N NaOH and 3 ml of H_2O was added to a solution of **2** (1.05 g, 5 mmol) in 32 ml of dioxane. The solution was refluxed for 3.5 h and then treated as above to give aniline (0.15 g, 32%), **2** (0.58 g, 55%) and acetanilide (0.19 g, 28%), which did not contain any $PhNHCOCD_3$.

Hydrolysis of 1 in the Presence of BzOH and BzONa Compound **1** (1.57 g, 5 mmol), BzOH (0.61 g, 5 mmol) and BzONa (0.72 g, 5 mmol) were dissolved in a mixture of 32 ml of dioxane and 8 ml of H_2O. The whole was refluxed for 3.5 h. Then 40 ml of 7% $NaHCO_3$ was added to the solution, and the mixture was concentrated under reduced pressure. The distillate, after being made acidic by addition of HCl, was evaporated to dryness, and the remaining material was treated as usual to give aniline (0.12 g, 25%). Water was added to the residue, and the mixture was extracted with ether. The aqueous layer was treated as usual to give 1.46 g of BzOH. Subtracting the amount of BzOH used as the catalyst, the amount of BzOH formed in the reaction was calculated to be 0.24 g (39%). The ether layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to preparative thin layer chromatography (TLC) (silica gel) with benzene–AcOEt (5 : 1) to give **2** (0.11 g, 10%), acetanilide (0.40 g, 59%) and benzanilide (0.17 g, 17%).

The sample for HPLC analysis was prepared as follows: a solution of BzOH (0.3503 g, 2.5 mmol) and BzONa (0.3603 g, 2.5 mmol) in a mixture of 4 ml of H_2O and 5 ml of dioxane was added to a solution of **1** (0.7855 g, 2.5 mmol) in 20 ml of dioxane, and 2.25 ml of H_2O was added to the

solution. The whole was refluxed for 3.5 h. Then 10 ml of 7% $NaHCO_3$ was added to the solution, and the mixture was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with ether. The aqueous layer was treated as usual to give BzOH (0.2148 g, 70%). The ether layer was dried over Na_2SO_4, and concentrated under reduced pressure. A part of a CH_3CN solution of the residue was subjected to HPLC on a reversed-phase column (μ Bondapak C18) with CH_3CN–0.02 M K_2HPO_4 (1 : 1). The results are described in the main text.

Hydrolysis of *N*-Benzoyl-*N*-acetylaniline in the Presence of AcOH and AcONa Acetic acid (0.15 g, 2.5 mmol) and AcONa·$3H_2O$ (0.34 g, 2.5 mmol) were dissolved in 5 ml of H_2O, and 1 ml of the solution was added to a solution of *N*-benzoyl-*N*-acetylaniline (0.12 g, 0.5 mmol) in 4 ml of dioxane. The whole was refluxed for 3.5 h. Then 30 ml of 7% $NaHCO_3$ was added to the solution, and the mixture was concentrated under reduced pressure. The distillate, after being made acidic by addition of HCl, was concentrated under reduced pressure. No organic material remained. Water was added to the residue, and the mixture was extracted with $CHCl_3$. The aqueous layer was treated as usual to give BzOH (0.02 g, 33%). The $CHCl_3$ layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to preparative TLC (silica gel) with benzene–AcOEt (5 : 1) to give benzanilide (0.03 g, 30%), acetanilide (0.03 g, 44%) and *N*-benzoyl-*N*-acetylaniline (0.02 g, 17%).

The sample used for HPLC analysis was prepared as follows: AcOH (0.0600 g, 1 mmol), 1.5 ml of H_2O and 0.5 ml of 1 N NaOH were added to a solution of *N*-benzoyl-*N*-acetylaniline (0.1201 g, 0.5 mmol) in 8 ml of dioxane. The whole was refluxed for 3.5 h, and 10 ml of 7% $NaHCO_3$ was added to the solution. The mixture was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with $CHCl_3$. The $NaHCO_3$ layer was treated as usual to give BzOH (0.0079 g, 13%). The $CHCl_3$ layer was dried over Na_2SO_4, and concentrated under reduced pressure. A part of a CH_3CN solution of the residue was subjected to HPLC on a reversed-phase column (μ Bondapak C18) with CH_3CN–0.02 M K_2HPO_4 (2 : 1). The ratio of PhNHBz : PhNHAc : PhNBzAc was 7 : 11 : 81.

Reaction of 1 and *p*-Methoxybenzoic Acid A solution of **1** (1.05 g, 3.3 mmol) and *p*-methoxybenzoic acid (0.51 g, 3.3 mmol) in 10 ml of anhydrous dioxane was refluxed for 2 h and allowed to cool to room temperature. *m*-Chloroaniline (0.84 g, 6.6 mmol) was added to the reaction mixture, and the whole was allowed to stand overnight. The whole was concentrated under reduced pressure, and the residue was dissolved in ether. The ether solution was extracted with 20 ml of 7% $NaHCO_3$. The $NaHCO_3$ layer was treated as usual to give 0.47 g of a mixture of benzoic acid and *p*-methoxybenzoic acid. The ether layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to preparative TLC (silica gel) with benzene–AcOEt (5 : 1) and $CHCl_3$–petroleum benzin (7 : 3) to give **2** (0.09 g, 13%), acetanilide (0.15 g, 33%), *N*-benzoyl-*m*-chloroaniline (0.11 g, 13%), *N*-(*p*-methoxybenzoyl)aniline (0.11 g, 15%), benzanilide (0.08 g, 12%), *N*-(*p*-methoxybenzoyl)-*m*-chloroaniline (0.11 g, 13%) and *N*-acetyl-*m*-chloroaniline (0.03 g, 5%).

N^1-Benzoyl-N^1,N^2-diphenylformamidine (7) A solution of BzCl (2.53 g, 18 mmol) in 20 ml of CH_2Cl_2 was added to a mixture of **8** (3.53 g, 18 mmol) in 30 ml of CH_2Cl_2 containing NaH (0.86 g, 36 mmol) under ice cooling. The reaction mixture was allowed to stand for 3 h at room temperature, then washed successively with 30 ml of 7% $NaHCO_3$ and H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was recrystallized from benzene–petroleum benzin to give 2.90 g (55%) of **7**. mp 114 °C. *Anal.* Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 79.77; H, 5.41; N, 9.48. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 8.98 (1H, s, 1-position).

Hydrolysis of 7 in the Presence of AcOH and AcONa A solution of AcOH (0.24 g, 4 mmol) and AcONa·$3H_2O$ (0.54 g, 4 mmol) in 10 ml of H_2O was added to a solution of **7** (1.21 g, 4 mmol) in 45 ml of dioxane. Then 2 ml of H_2O was added to the mixture to form a transparent solution. The whole was refluxed for 4.7 h, and 30 ml of 7% $NaHCO_3$ was added. The mixture was concentrated under reduced pressure. The distillate, after being made acidic by addition of HCl, was evaporated to dryness, and the remaining material was treated as usual to give aniline (0.07 g, 19%). Water was added to the residue, and the mixture was extracted with $CHCl_3$. The $NaHCO_3$ layer was treated as usual to give BzOH (0.02 g, 4%). The $CHCl_3$ layer was dried over Na_2SO_4, and concentrated under reduced pressure. Benzene was added to the residue, and the deposited precipitate, benzanilide, was collected. The filtrate was concentrated under reduced pressure, and the residue was subjected to column chromatography (Al_2O_3) with benzene to give benzanilide (total yield, 0.72 g, 91%), acetanilide (0.04 g, 7%) and formanilide (0.32 g, 63%).

Hydrolysis of 8 in the Presence of AcOH and AcONa A solution of AcOH (0.20 g, 3.3 mmol) and AcONa·$3H_2O$ (0.45 g, 3.3 mmol) in 6 ml of H_2O was added to a solution of **8** (0.65 g, 3.3 mmol) in 24 ml of dioxane. The whole was warmed at 40 °C for 6 h and 30 ml of 7% $NaHCO_3$ was added. The mixture was concentrated under reduced pressure. The distillate, after being made acidic by addition of HCl, was evaporated to dryness. The remaining material was treated as usual to give aniline. The residue was extracted with ether, and the ether layer was extracted with 20 ml of 1 N HCl. The deposited precipitate, the hydrochloride of **8**, was collected, and treated as usual to give a trace of **8**. The ether layer of the filtrate was extracted once more with 1 N HCl, and the combined HCl layer was treated as usual to give aniline (total yield, 0.18 g, 58%). The ether layer was dried over Na_2SO_4, and concentrated under reduced pressure to give formanilide (0.28 g, 69%).

Hydrolysis of 6a, b in the Presence of $ClCH_2COOH$ and $ClCH_2COONa$ A solution of $ClCH_2COOH$ (0.47 g, 5 mmol) in 2.5 ml of H_2O and 2.5 ml of 1 N NaOH were added to a solution of **6a**, **b** (2.5 mmol) in 20 ml of dioxane. The whole was refluxed (**6a**, for 27 h; **6b**, for 19 h), and 15 ml of 7% $NaHCO_3$ was added to the solution. The mixture was concentrated under reduced pressure. The distillate, after being made acidic by addition of HCl, was evaporated to dryness. No organic material remained. Water was added to the residue, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was extracted with 2 N NaOH. The NaOH layer was treated as usual to give *N*-tosylarylamine. The $CHCl_3$ layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to preparative TLC (silica gel) with benzene–AcOEt (5 : 1) to give *N*-acetylarylamine, *N*-(chloroacetyl)arylamine and *N*-(hydroxyacetyl)arylamine. A small amount of compound **9**, melting at 101 °C, was obtained by the hydrolysis of **6b**. MS of **9** showed a peak at *m/z* 207 (M^+). *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 63.74; H, 6.32; N, 6.79. Found; C, 63.75; H, 6.36; N, 6.94. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.19 (3H, s, CH_3CO), 2.31 (3H, s, aryl CH_3), 4.65 (2H, s, CH_2), 7.15 (2H, d, J=8 Hz, *m*-position), 7.40 (2H, d, J=8 Hz, *o*-position) and 7.97 (1H, br s, NH). The results (yields of ArNHAc, ArNHTs, $ArNHCOCH_2Cl$ and $ArNHCOCH_2OH$) were as follows: **6a**, 0.30 g, (88%), 0.53 g (86%), 0.03 g (7%), 0.02 g (5%); **6b**, 0.34 g (91%), 0.60 g (92%), 0.02 g (4%), 0.02 g (5%).

Hydrolysis of 6b in the Presence of $HOCH_2COOH$ and $HOCH_2COONa$ A solution of $HOCH_2COOH$ (0.38 g, 5 mmol) in 6.5 ml of H_2O and 2.5 ml of 1 N NaOH were added to a solution of **6b** (0.98 g, 2.5 mmol) in 30 ml of dioxane. The whole was refluxed for 30 h, and 20 ml of $NaHCO_3$ was added to the mixture. The mixture was concentrated under reduced pressure, and the residue was extracted with $CHCl_3$. The $CHCl_3$ solution was extracted with 2 N NaOH. The NaOH layer was treated as usual to give *N*-tosyl-*p*-toluidine (0.47 g, 72%). The $CHCl_3$ layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to preparative TLC (silica gel) with benzene–AcOEt (5 : 1) to give **6b** (0.22 g, 22%), *N*-acetyl-*p*-toluidine (0.10 g, 27%), *N*-(hydroxyacetyl)-*p*-toluidine (0.02 g, 5%) and **9** (0.03 g).

***N*-(Acetoxyacetyl)-*p*-toluidine (9)** A solution of acetoxyacetyl chloride[6] (7.51 g, 55 mmol) in 20 ml of anhydrous benzene was added to a solution of *p*-toluidine (5.36 g, 50 mmol) and Et_3N (5.57 g, 55 mmol) in 30 ml of anhydrous benzene. The reaction mixture was allowed to stand overnight at room temperature. Benzene was removed under reduced pressure, and 50 ml of H_2O was added to the residue. The deposited precipitate was collected, washed with H_2O, and recrystallized from benzene to give **9** (8.24 g, 80%). The sample was identical with that obtained in the hydrolysis of **6b** in the presence of $HOCH_2COOH$ and $HOCH_2COONa$ (preceding section) on the basis of mixed melting point measurement and comparison of their IR spectra.

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