Amidines. VI. 1,3-*N*,*N*-Acylotropic Amidine Rearrangement of N^1-Acyl Derivatives of N^1,N^2-Disubstituted Amidine

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N^1-Tosyl-N^1,N^2-diarylacetamidines (1) undergo nucleophilic attack of *N*-tosylamide anion at the amidine central carbon, and the less basic *N*-tosylamido group is expelled from the intermediate, resulting in an amide exchange reaction. Reaction of 1 and *N*-arylcarboxamide afforded N^1-acyl-N^1,N^2-diarylacetamidine (2). N^1-(*p*-Chlorobenzoyl)-N^1-(*p*-methoxyphenyl)-N^2-(*p*-chlorophenyl)acetamidine (2a) could not be obtained as such, but was obtained as an equilibrium mixture of 2a and N^1-(*p*-chlorobenzoyl)-N^1-(*p*-chlorophenyl)-N^2-(*p*-methoxyphenyl)acetamidine (2a') owing to rapid 1,3-*N*,*N*-acylotropic rearrangement.

N^1-Acyl derivatives of unsymmetrical N^1,N^2-disubstituted formamidines could be isolated as such, showing that 1,3-*N*,*N*-acyl migration takes place more slowly in the acylated formamidine system. An acyl derivative of formamidine in which the acyl group is attached at the less basic nitrogen of amidine underwent 1,3-*N*,*N*-acyl migration to give another acyl derivative at elevated temperature.

Reaction of N^1-tosyl-N^1-(*p*-nitrophenyl)-N^2-(*m*-nitrophenyl)acetamidine (1h) and *N*-acylarylamines gave N^1-acyl-N^1-aryl-N^2-(*m*-nitrophenyl)acetamidines (2) which underwent alcoholysis to give carboxylic acid ester and N^1-aryl-N^2-(*m*-nitrophenyl)acetamidines (3) at room temperature, and the latter was hydrolyzed to give arylamines and *N*-acetyl-*m*-nitroaniline on heating in aqueous tetrahydrofuran solution in the presence of acetic acid. Thus, the alcoholysis of *N*-acylarylamines was achieved under mild conditions.

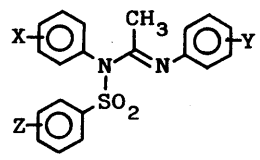
Keywords *N*-tosylacetamidine; *N*-acylacetamidine; *N*-acylformamidine; amide exchange reaction; 1,3-*N*,*N*-acyl migration; 1,3-*N*,*N*-tosyl migration; alcoholysis; hydrolysis; *N*-acylarylamine

In the preceding paper[1] we reported a preparative approach to N^1-acyl-N^1,N^2-diarylacetamidines (**2**) through an amide exchange of the sulfonamido group of N^1-(substituted benzenesulfonyl)-N^1,N^2-diarylacetamidines by an *N*-acylamino group. N^1-(*p*-Nitrobenzenesulfonyl)-N^1,N^2-diarylacetamidines prepared in an attempt to enhance the electrophilic character of the amidine central carbon, however, underwent Smiles rearrangement to give N^1-(*p*-nitrophenyl)-N^1,N^2-diarylacetamidines, showing that enhancement of the electron-withdrawing nature of the benzenesulfonyl group is of limited use as a means to promote the amide exchange reaction.

In this work, reaction of *N*-tosylarylamines or *N*-acylarylamines and N^1-tosyl-N^1,N^2-diarylacetamidines (**1**) carrying an electron-withdrawing substituent on the N^1-aryl group was examined. It was found that 1,3-*N*,*N*-acylotropic amidine rearrangement easily occurs in *N*-acyl derivatives of unsymmetrical N^1,N^2-diarylacetamidines.

1,3-*N*,*N*-Acylotropic Amidine Rearrangement Willi[2] reported that the acid dissociation constant of *N*-benzenesulfonyl-*p*-nitroaniline is 130 times larger than that of *N*-benzenesulfonylaniline, while the dissociation constant of *N*-(*p*-nitrobenzenesulfonyl)aniline is only 8 times larger than that of *N*-benzenesulfonylaniline. Therefore, among the three aryl substituents affecting the electrophilicity of the amidine central carbon (X, Y and Z, Chart 1), the effect of substituent Z was examined in the preceding work.[1] Substituent X might be expected to have a larger influence on the electrophilic character of the amidine central carbon.

N^1-Tosyl-N^1-(*p*-nitrophenyl)-N^2-(*p*-methylphenyl)acetamidine (**1a**) was prepared by Beckmann rearrangement[3,4] of *p*-methylacetophenoxime tosylate in the presence of the sodium salt of *N*-tosyl-*p*-nitroaniline. The structure of **1a** was confirmed by alcoholysis in ethanol solution containing sodium ethoxide, which gave *N*-tosyl-*p*-nitroaniline and ethyl *N*-(*p*-methylphenyl)acetimidate in good yields. N^1-Tosyl-N^1-(*p*-chlorophenyl)-N^2-(*p*-methylphenyl)acetamidine (**1b**) was obtained in 76% yield when a dimethyl sulfoxide (DMSO) solution of **1a** and the sodium salt of *N*-tosyl-*p*-chloroaniline was heated at 90 °C for 2.5 h, showing that the amide exchange reaction of the *N*-tosylamido group takes place at the amidine central carbon of N^1-tosyl-N^1,N^2-diarylacetamidines (**1**) in the direction in which the more acidic *N*-tosylamido group is expelled from the intermediate (Chart 1). Compound **1b** could not be prepar-



1: Z = *p*-CH_3

	X	Y		X	Y		X	Y
a	*p*-NO_2,	*p*-CH_3	d	*p*-NO_2,	*p*-CH_3O	g	*p*-CH_3,	*p*-NO_2
b	*p*-Cl,	*p*-CH_3	e	*p*-NO_2,	*p*-NO_2	h	*p*-NO_2,	*m*-NO_2
c	*p*-NO_2,	*p*-Cl	f	*p*-Cl,	*p*-NO_2	i	*m*-NO_2,	*p*-NO_2

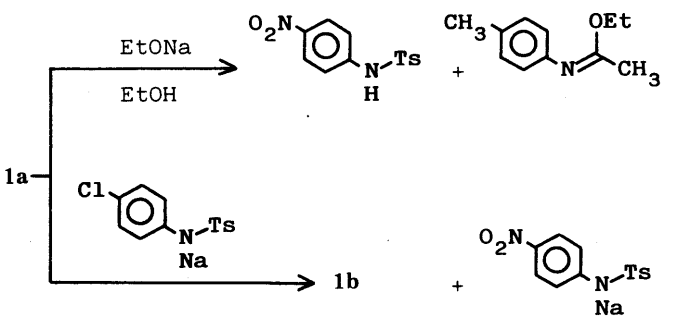


Chart 1

ed by the reaction of N^1-tosyl-N^1,N^2-di(p-methylphenyl)-acetamidine and the sodium salt of N-tosyl-p-chloroaniline.[1)]

When a tetrahydrofuran (THF) solution of N^1-tosyl-N^1-(p-nitrophenyl)-N^2-(p-chlorophenyl)acetamidine (**1c**) and N-(p-chlorobenzoyl)-p-anisidine was allowed to stand for 1 d at room temperature in the presence of potassium *tert*-butoxide, a powdery material melting at 131 °C was obtained. The results of elemental analysis of the material were consistent with the values required for the molecular formula of $C_{22}H_{18}Cl_2N_2O_2$. The presumed structure of the material is N^1-(p-chlorobenzoyl)-N^1-(p-methoxyphenyl)-N^2-(p-chlorophenyl)acetamidine (**2a**, Chart 2). The product obtained from N^1-tosyl-N^1-(p-nitrophenyl)-N^2-(p-methoxyphenyl)acetamidine (**1d**) and N-(p-chlorobenzoyl)-p-chloroaniline was, however, identical with the product of the former reaction on the basis of comparison of their infrared (IR) spectra. The presumed structure of the product of the latter reaction is N^1-(p-chlorobenzoyl)-N^1-(p-chlorophenyl)-N^2-(p-methoxyphenyl)acetamidine (**2a'**, Chart 2). Acid hydrolysis of the product gave N-(p-chlorobenzoyl)-p-anisidine (23%), N-acetyl-p-chloroaniline (6%), N-(p-chlorobenzoyl)-p-chloroaniline (23%), N-acetyl-p-anisidine (6%) and a trace of p-anisidine (Chart 2).

The product of the reaction between **1c** and N-(p-chlorobenzoyl)-p-anisidine or between **1d** and N-(p-chlorobenzoyl)-p-chloroaniline was presumed to be a tautomeric mixture of **2a** and **2a'**. Presumably 1,3-N,N-acylotropic rearrangement occurs during the reaction. Minkin *et al.*[5)] reported 1,3-N,N-acylotropic rearrangement of N^1-benzoyl-N^1,N^2-diarylbenzamidines. They calculated that the rate constant of migration of the benzoyl group of N^1-benzoyl-N^1,N^2-di(p-methylphenyl)benzamidine is $1.17 \times 10^{-5}\ s^{-1}$ at 25 °C in o-dichlorobenzene solution on the basis of ^{1}H nuclear magnetic resonance (^{1}H-NMR) evidence. They claimed that the reaction is an intramolecular acylotropic

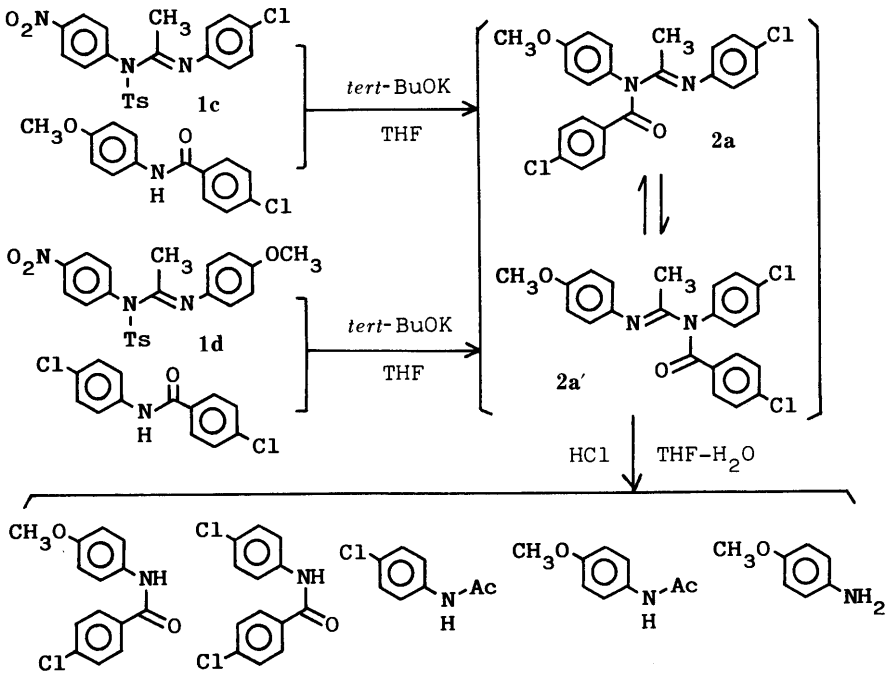


Chart 2

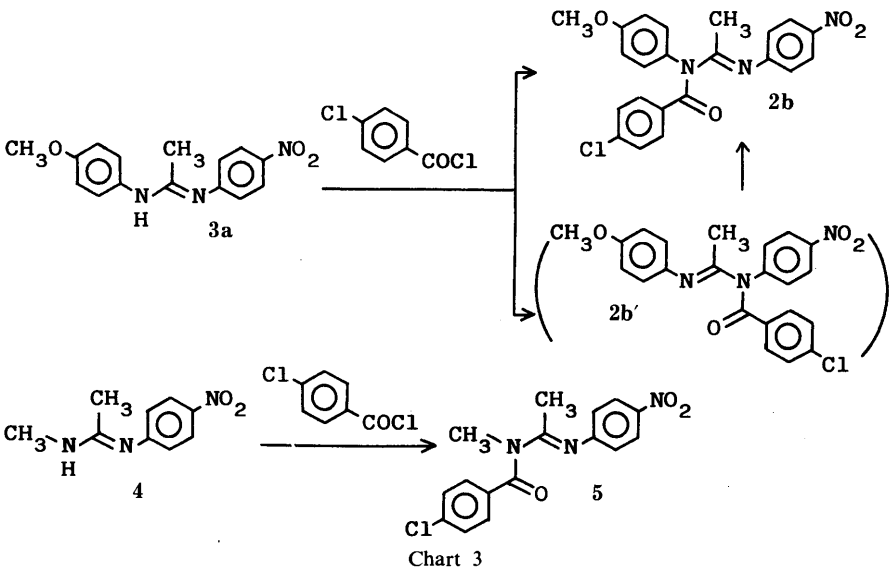


Chart 3

rearrangement through a tetrahedral intermediate, and occurs more slowly in formamidine derivatives.

However, *p*-chlorobenzoylation of unsymmetrical acetamidines, N^1-(*p*-methoxylphenyl)-N^2-(*p*-nitrophenyl)acetamidine (**3a**) or N^1-methyl-N^2-(*p*-nitrophenyl)acetamidine (**4**), was proved to afford a single product. Thus, reaction of **3a** and *p*-chlorobenzoyl chloride gave a product melting at 116 °C. Acid hydrolysis of the product gave *N*-(*p*-chlorobenzoyl)-*p*-anisidine and *N*-acetyl-*p*-nitroaniline. *N*-(*p*-Chlorobenzoyl)-*p*-nitroaniline and *N*-acetyl-*p*-anisidine could not be detected in the hydrolysis mixture. The structure of the product was determined to be N^1-(*p*-chlorobenzoyl)-N^1-(*p*-methoxyphenyl)-N^2-(*p*-nitrophenyl)acetamidine (**2b**) rather than N^1-(*p*-chlorobenzoyl)-N^1-(*p*-nitrophenyl)-N^2-(*p*-methoxyphenyl)acetamidine (**2b′**). The large difference in basicity of the two nitrogens of the amidine causes one-sided bonding of the acyl group to the more basic nitrogen atom (Chart 3). Reaction of **4** and *p*-chlorobenzoyl chloride gave N^1-(*p*-chlorobenzoyl)-N^1-methyl-N^2-(*p*-nitrophenyl)acetamidine (**5**) as a single product. The structure of **5** was confirmed by ^{1}H-NMR evidence, *i.e.*, the signals of the *o*-positions of the *p*-nitrophenyl group appeared at high applied magnetic field (δ 6.75, as a doublet, J=9 Hz)[6] (Chart 3).

Acyl migration of N^1-acyl-N^1,N^2-diarylformamidine proceeds much more slowly than that of acetamidine derivatives. The ^{1}H-NMR spectrum of the crude product of the reaction between N^1-(*p*-methoxyphenyl)-N^2-(*p*-nitrophenyl)formamidine (**6a**) and *p*-chlorobenzoyl chloride showed two signals due to the amidine central position at δ 9.02 and 8.92 in a ratio of 3.5 : 1. A product melting at 185 °C was isolated from the ether-insoluble part of the crude product. Acid hydrolysis of the product gave *N*-(*p*-chlorobenzoyl)-*p*-anisidine, *N*-formyl-*p*-nitroaniline and *p*-nitroaniline. Thus, the structure of the product was determined to be N^1-(*p*-chlorobenzoyl)-N^1-(*p*-methoxyphenyl)-N^2-(*p*-nitrophenyl)formamidine (**7a**). From the mother liquor, another product melting at 132 °C was isolated by repeated recrystallization from petroleum benzin. Acid hydrolysis of the product gave *N*-(*p*-chlorobenzoyl)-*p*-nitroaniline and *N*-formyl-*p*-anisidine. Thus, the structure of the product was determined to be N^1-(*p*-chlorobenzoyl)-N^1-(*p*-nitrophenyl)-N^2-(*p*-methoxyphenyl)formamidine (**7b**). The structures of **7a** and **7b** were further supported by their ^{1}H-NMR spectra (Chart 4). The assignment of signals was confirmed by nuclear Overhauser effect (NOE) and internuclear double resonance (INDOR) techniques. In Chart 4, the chemical shift of each signal is given in δ (ppm).

p-Chlorobenzoylation of **6a** was proved to afford a mixture of **7a** and **7b**. Compound **7b** was converted into **7a** on refluxing its benzene solution for 10 h, while **7a** showed no change on the same treatment (Chart 4). *p*-Chlorobenzoylation of **3a** gave **2b** as a sole product, while the same reaction of **6a** afforded two products acylated at both nitrogen atoms. Probably **2b′** was formed together with **2b** in the initial stage of the reaction between **3a** and *p*-chlorobenzoyl chloride, and the **2b′** was converted into **2b** by rapid 1,3-*N*,*N*-acyl migration (Chart 3).

p-Chlorobenzoylation of N^1-(*p*-methylbenzyl)-N^2-(*p*-nitrophenyl)formamidine (**8**) also gave two products. The structures of the products were determined to be N^1-(*p*-chlorobenzoyl)-N^1-(*p*-methylbenzyl)-N^2-(*p*-nitrophenyl)-formamidine (**9a**) and N^1-(*p*-chlorobenzoyl)-N^1-(*p*-nitrophenyl)-N^2-(*p*-methylbenzyl)formamidine (**9b**) on the basis of the results of acid hydrolysis and of their ^{1}H-NMR spectra, as shown in Chart 5. The chemical shift of each signal is given in δ (ppm) in Chart 5. Acylation of **6a** or **8** is in contrast to that of **3a** or **4**.

According to Minkin *et al.*[5] acyl migration of N^1-acyl-N^1,N^2-diarylamidines proceeds through a tetrahedral intermediate involving a four-membered ring (Chart 6). They attributed the difference in reactivity between *N*-acylbenzamidines and *N*-acylformamidines to delocalization of the positive charge of the intermediate by conjugation with a phenyl group attached to the amidine central carbon in benzamidine derivatives. Acyl migration of N^1-acyl-N^1,N^2-diarylacetamidines proceeded much faster than that of N^1-acylformamidines. Probably a methyl group attached to the amidine central carbon of acetamidine stabilized the inter-

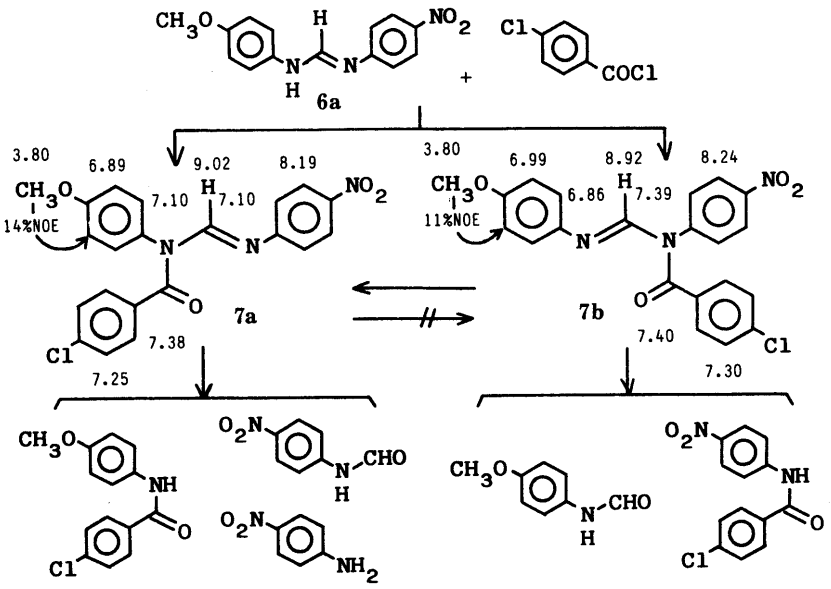


Chart 4

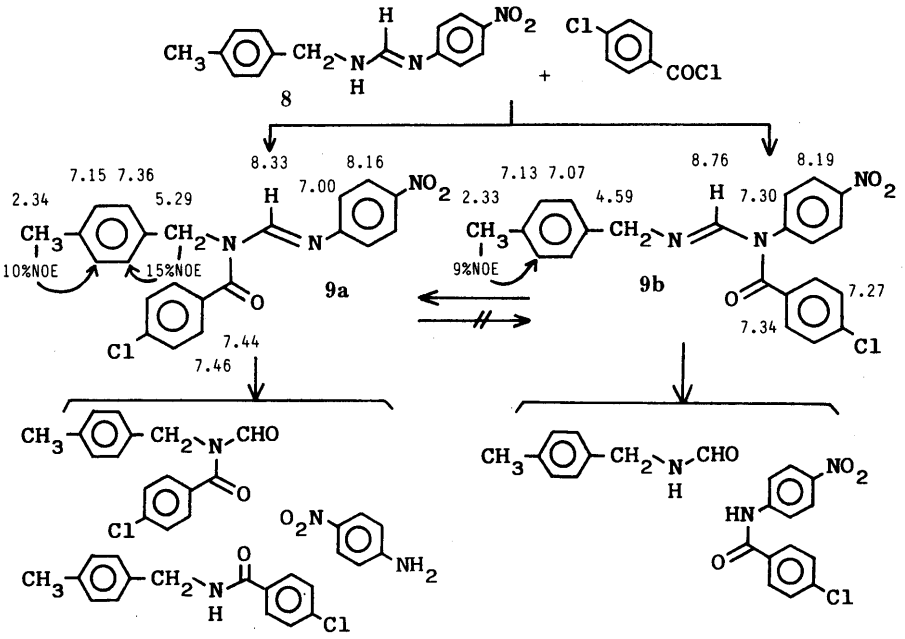


Chart 5

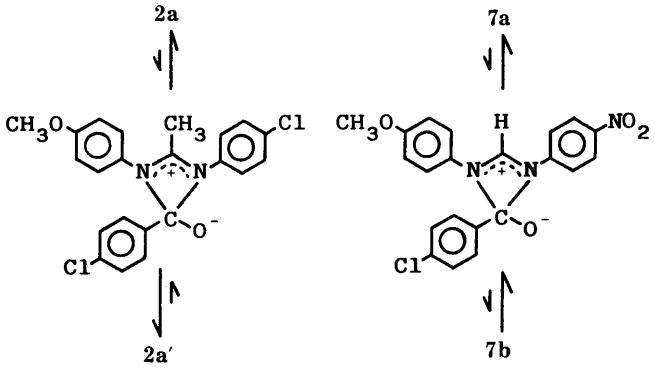


Chart 6

mediate by hyperconjugation with the positive charge in the conjugated amidine cation (Chart 6).

Alcoholysis of *N*-Arylcarboxamides under Mild Conditions *via* N^1-Acyl-N^1,N^2-diarylacetamidines N^1-Acyl-N^1,N^2-diarylacetamidines (**2**) undergo alkaline hydrolysis and alcoholysis at room temperature to give N^1,N^2-diarylacetamidines (**3**) and carboxylic acid or its ester,[3] and the former compounds, especially those carrying an electron-withdrawing N^2-aryl group, are easily hydrolyzed in aqueous acetic acid solution to give the more basic amine and the acetyl derivative of the less basic amine.[7] Amide exchange reaction of the tosylamino group of N^1-tosyl-N^1,N^2-diarylacetamidines (**1**) with an acylamino group can be expected to provide a new method for hydrolysis or alcoholysis of carboxamides under mild conditions.[1] For this purpose, N^1-tosyl-N^1,N^2-di(*p*-nitrophenyl)acetamidine (**1e**), which carries electron-withdrawing substituents on both the N^1- and N^2-aryl groups, appears to be a suitable starting material for the hydrolysis of carboxamides by the above-mentioned method.

Compound **1e** is, however, scarcely soluble in any of the solvents examined.[6] To avoid this difficulty, N^1-tosyl-N^1-(*p*-chlorophenyl)-N^2-(*p*-nitrophenyl)acetamidine (**1f**) was also examined for the purpose.

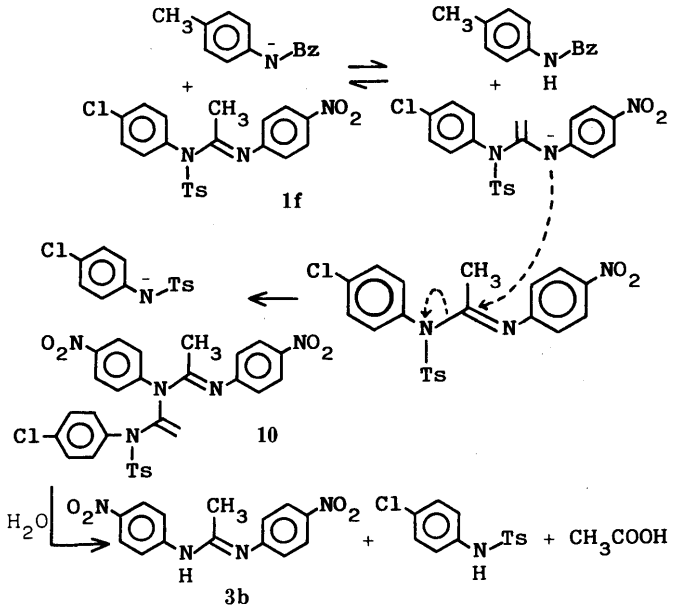


Chart 7

The reaction of **1f** and the potassium salt of *N*-benzoyl-*p*-toluidine gave *N*-tosyl-*p*-chloroaniline in quantitative yield, together with a small amount of N^1,N^2-di(*p*-nitrophenyl)acetamidine (**3b**), N^1-Benzoyl-N^1-(*p*-methylphenyl)-N^2-(*p*-nitrophenyl)acetamidine, however, could not be detected in the reaction mixture, and *N*-benzoyl-*p*-toluidine was recovered in almost quantitative yield. The reaction of **1e** and the potassium salt of *N*-benzoyl-*p*-toluidine in dimethylformamide (DMF) solution gave similar results. The mechanism of the degradation of **1f** is probably as follows: a proton of the amidine central methyl group of **1f** is abstracted by base to give the conjugate base of **1f**, and attack of the latter at the central carbon of another molecule of **1f** and subsequent expulsion of *N*-tosyl-*p*-chloroanilide anion affords *N*-[1-{1-(*N*-tosyl-*N*-*p*-chlorophenyl)amino}ethenyl]-*N*,*N*′-di(*p*-nitrophenyl)ethanim-

idamide (**10**). A trace of water would be contained in the medium, and would hydrolyze **10** to give **3b**, *N*-tosyl-*p*-chloroaniline and acetic acid (Chart 7).

When a DMF solution of **1e** and the sodium salt of *N*-tosyl-*p*-toluidine was heated at 90 °C for 2 h, N^1-tosyl-N^1-(*p*-methylphenyl)-N^2-(*p*-nitrophenyl)acetamidine (**1g**) was obtained. *N*-Tosyl-*p*-toluidide anion attacked the amidine central carbon of **1e** while the more basic *N*-benzoyl-*p*-toluidide anion abstracted a proton from the methyl group of **1e**.

The preparation of N^1-tosyl-N^1-(*p*-nitrophenyl)-N^2-(*m*-nitrophenyl)acetamidine (**1h**) was attempted to obtain a better material for the hydrolysis of carboxamides. When an anisole solution of *m*-nitroacetophenoxime tosylate was refluxed for 5 h in the presence of the sodium salt of *N*-tosyl-*p*-nitroaniline, two products melting at 194 °C and at 220 °C were obtained. The results of elemental analysis of the products were both consistent with the values required for the molecular formula of $C_{21}H_{18}N_4O_6S$. The structures of the products were determined to be **1h** (mp 194 °C) and N^1-tosyl-N^1-(*m*-nitrophenyl)-N^2-(*p*-nitrophenyl)acetamidine (**1i**) (mp 220 °C) from the results of alcoholysis, *i.e.*, the former was alcoholyzed in ethanol solution to give *N*-tosyl-*p*-nitroaniline and ethyl *N*-(*m*-nitrophenyl)acetimidate in the presence of sodium ethoxide, while the latter gave *N*-tosyl-*m*-nitroaniline and ethyl *N*-(*p*-nitrophenyl)acetimidate by the same reaction. 1,3-*N*,*N*-Tosyl migration was proved to take place in N^1-tosyl-N^1,N^2-diarylacetamidine (**1**) at high temperature (Chart 8). When a DMF solution of *m*-nitroacetophenoxime tosylate was heated at 90 °C for 2 h in the presence of the sodium salt of *N*-tosyl-*p*-nitroaniline, **1h** was obtained as a sole product, and when a xylene solution of *p*-nitroacetophenoxime tosylate was refluxed for 5.5 h in the presence of the sodium salt of *N*-tosyl-*m*-nitroaniline, **1i** was obtained as a sole product. When an anisole solution of **1h** was refluxed for 12 h, **1i** (16%) was isolated from the darkened mixture, and **1h** could not be detected in the mixture. Only the starting material (24%) was isolated when **1i** was treated under the same conditions. Compound **1g** was obtained when a xylene solution of **1a** was refluxed for 20 h, while **1g** showed no change under the same treatment. Tosyl migration in N^1-tosyl-N^1,N^2-diarylacetamidine (**1**) was proved to take place so as to afford a tosyl derivative in which the tosyl group is attached to the more basic nitrogen atom of the amidine. When a xylene solution of acetoxime tosylate was refluxed for 8 h in the presence of the sodium salt of *N*-tosyl-*p*-nitroaniline, N^1-tosyl-N^1-methyl-N^2-(*p*-nitrophenyl)acetamidine (**11**) was isolated from the reaction mixture as a sole product, showing that tosyl migration took place completely during the reaction (Chart 8).

Compound **1h** was found to be applicable for the alcoholysis of *N*-arylcarboxamides. The reaction of **1h** and *N*-(*p*-chlorobenzoyl)-*p*-anisidine in the presence of potassium *tert*-butoxide gave N^1-(*p*-chlorobenzoyl)-N^1-(*p*-methoxyphenyl)-N^2-(*m*-nitrophenyl)acetamidine (**2c**). N^1-(*p*-Chlorobenzoyl)-N^1-(*p*-methylphenyl)-N^2-(*m*-nitrophenyl)acetamidine (**2d**) was also obtained in a similar manner. When an ethanol–THF solution of **2c** was kept for 1 d at room temperature in the presence of sodium ethoxide, N^1-(*p*-

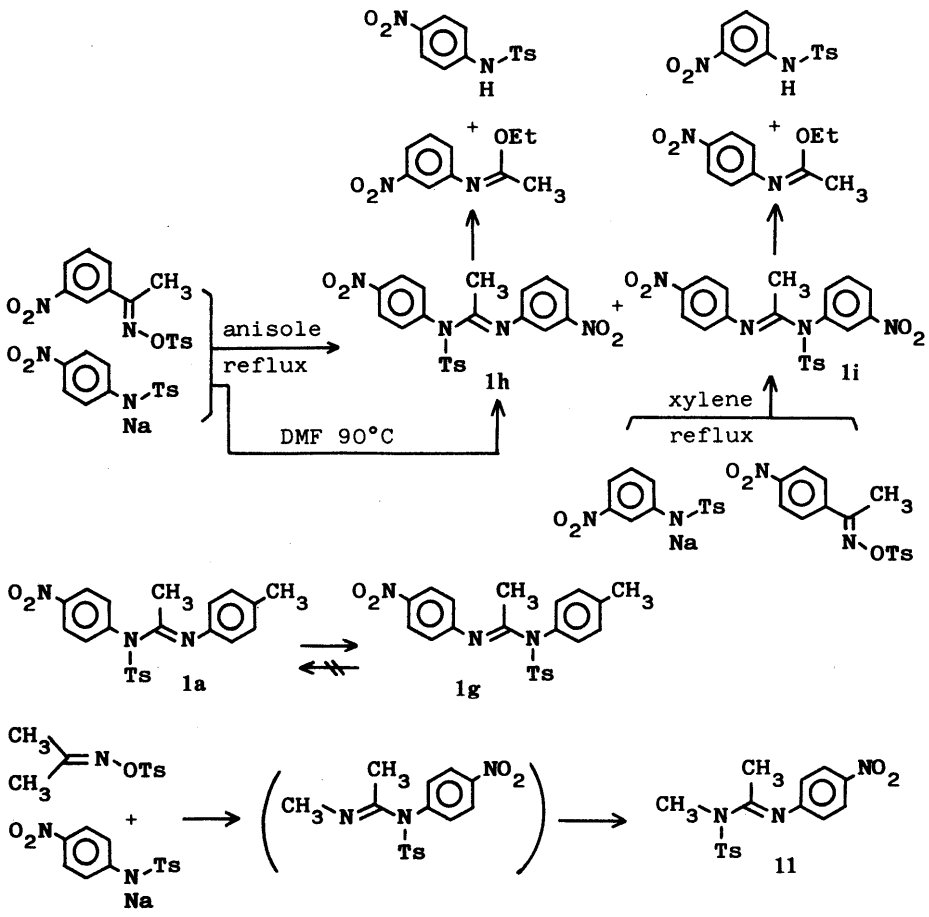
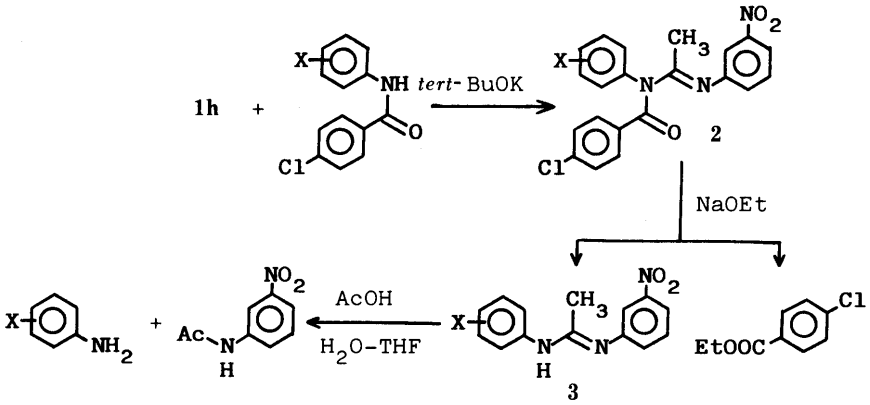


Chart 8



X: 2c and 3c, p-CH_3O; 2d and 3d, p-CH_3; 2e and 3e, o-CH_3

Chart 9

methoxyphenyl)-N^2-(*m*-nitrophenyl)acetamidine (**3c**) and ethyl *p*-chlorobenzoate were obtained. Compound **2d** was also alcoholyzed to give N^1-(*p*-methylphenyl)-N^2-(*m*-nitrophenyl)acetamidine (**3d**) and ethyl *p*-chlorobenzoate under the same conditions. Alkaline hydrolysis of **2d** also proceeded at room temperature, *i.e.*, **3d** and *p*-chlorobenzoic acid were obtained when a mixture of THF solution of **2d** and aqueous sodium hydroxide was stirred for 2 d. Reaction of **1h** and *N*-(*p*-chlorobenzoyl)-*o*-toluidine in the presence of potassium *tert*-butoxide gave N^1-(*p*-chlorobenzoyl)-N^1-(*o*-methylphenyl)-N^2-(*m*-nitrophenyl)acetamidine (**2e**), which underwent alcoholysis to give N^1-(*o*-methylphenyl)-N^2-(*m*-nitrophenyl)acetamidine (**3e**) and ethyl *p*-chlorobenzoate (Chart 9).

In a previous paper[7] we reported a preparative route to unsymmetrical N^1-aryl-N^2-(*p*-nitrophenyl)acetamidines by the reaction of *p*-nitroaniline and N^1-tosyl-N^1,N^2-diarylacetamidines (**1**) under basic conditions. Unsymmetrical N^1-aryl-N^2-(*m*-nitrophenyl)acetamidines (**3**) could not be prepared by this method because *m*-nitroaniline was polymerized in the presence of potassium *tert*-butoxide. The reaction of **1h** and *N*-acylarylamine and subsequent alcoholysis of N^1-acyl-N^1-aryl-N^2-(*m*-nitrophenyl)acetamidines (**2**) formed provides a preparative method for unsymmetrical N^1-aryl-N^2-(*m*-nitrophenyl)acetamidines (**3**).

Hydrolysis of **3c** was achieved by heating under reflux of an aqueous THF solution of **3c** in the presence of acetic acid to give *p*-anisidine and *N*-acetyl-*m*-nitroaniline. A small amount of *N*-acetyl-*p*-anisidine was detected in the reaction mixture in contrast to the acid hydrolysis of **3a** which proceeded one-sidedly to give *p*-anisidine and *N*-acetyl-*p*-nitroaniline.[7] Hydrolysis of **3d** also proceeded to give *p*-toluidine, *N*-acetyl-*m*-nitroaniline and a small amount of *N*-acetyl-*p*-toluidine under the same conditions. Hydrolysis of sterically hindered **3e** proceeded with some difficulty to give *o*-toluidine and *N*-acetyl-*m*-nitroaniline in relatively low yields under the same conditions.

One-pot alcoholysis of *N*-(*p*-chlorobenzoyl)-*p*-toluidine was achieved *via* **2d** and **3d** to give *p*-toluidine and ethyl *p*-chlorobenzoate (see Experimental section), showing that alcoholysis of *N*-arylcarboxamides could be performed under mild conditions.

Experimental

All melting points are uncorrected. The ^{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), triplet (t), double triplet (dt), double double doublet (ddd), multiplet (m) and broad (br).

Amines, *N*-acylamines, *N*-tosylamines, imidates, esters, carboxylic acids and amidines described in this section were identical with the corresponding authentic samples on the basis of mixed melting point measurement or comparison of their IR spectra. Compounds **1e**, **3a**, **4**, **6a** and **8** were prepared according to the previous paper.[6]

N-(*p*-Chlorobenzoyl)-*p*-methylbenzylamine was prepared from *p*-methylbenzylamine and *p*-chlorobenzoyl chloride by the usual method: mp 198 °C ($CHCl_3$). *Anal.* Calcd for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.43; N, 5.39. Found: C, 69.07; H, 5.39; N, 5.35. ^{1}H-NMR (DMSO-d_6, 60 MHz) δ: 2.27 (3H, s, CH_3), 4.45 (2H, d, J=8 Hz, CH_2), 7.17 (4H, s, $CH_3C_6\underline{H}_4$), 7.53 (2H, d, J=9 Hz, 3′- and 5′-positions), 7.92 (2H, d, J=9 Hz, 2′- and 6′-positions) and 9.05 (1H, br t, J=8 Hz, NH).

N-(*p*-Chlorobenzoyl)-*o*-toluidine was prepared from *o*-toluidine and *p*-chlorobenzoyl chloride by the usual method: mp 157 °C (EtOH). *Anal.* Calcd for $C_{14}H_{12}ClNO$: C, 68.44; H, 4.92; N, 5.70. Found: C, 68.27; H, 4.96; N, 5.73. ^{1}H-NMR (CD_3OD, 60 MHz) δ: 2.30 (3H, s, CH_3), 7.13—7.33 (4H, m, $CH_3C_6\underline{H}_4$), 7.50 (2H, d, J=9 Hz, 3′- and 5′-positions) and 7.93 (2H, d, J=9 Hz, 2′- and 6′-positions).

Preparation of 1a by Beckmann Rearrangement Tosyl chloride (19.1 g, 0.1 mol) was dissolved in 160 ml of THF. The solution was added to a mixture of *p*-methylacetophenoxime (14.9 g, 0.1 mol) and Et_3N (12.51 g, 0.12 mol) under ice-cooling. The whole was kept in an ice-box for 1 d. The mixture was filtered, and the filtrate was added to a mixture of the sodium salt of *N*-tosyl-*p*-nitroaniline (31.4 g, 0.1 mol) and 400 ml of THF with stirring. The mixture was refluxed for 2.5 h, and then filtered hot. The filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$, and the solution was washed with 1 N NaOH, dried over K_2CO_3, and concentrated under reduced pressure. The residue was washed with a small amount of ether, and recrystallized from AcOEt to give 23.80 g (56%) of **1a**. mp 189 °C. *Anal.* Calcd for $C_{22}H_{21}N_3O_4S$: C, 62.40; H, 5.00; N, 9.92. Found: C, 62.50; H, 5.00; N, 10.01. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.78 (3H, s, 2-position), 2.30 (3H, s, CH_3 of N^2-aryl), 2.43 (3H, s, tosyl CH_3), 6.57 (2H, d, J=8 Hz, 2″- and 6″-positions), 7.10 (2H, d, J=8 Hz, 3″- and 5″-positions), 7.27 (2H, d, J=8 Hz, 3‴- and 5‴-positions), 7.53 (2H, d, J=9 Hz, 2′- and 6′-positions), 7.75 (2H, d, J=8 Hz, 2‴- and 6‴-positions) and 8.29 (2H, d, J=9 Hz, 3′- and 5′-positions).

Alcoholysis of 1a Compound **1a** (2.12 g, 5 mmol) was dissolved in 50 ml of THF. An NaOEt solution (prepared from 0.46 g of Na and 25 ml of EtOH) was added to the THF solution and additional 100 ml of EtOH was added to the mixture. The whole was warmed at 40 °C for a short time to dissolve the precipitate, and was kept for 3 d at room temperature. The mixture was saturated with CO_2, and concentrated under reduced pressure. Ether and H_2O were added to the residue, and the ether layer was extracted with 1 N NaOH. The NaOH layer was treated as usual to give 1.13 g (77%) of *N*-tosyl-*p*-nitroaniline. The ether layer was dried over Na_2SO_4, and concentrated under reduced pressure. A small amount of ether was added to the residue, and the precipitate was collected to give 0.08 g (4%) of the recovered starting material. The filtrate was concentrated under reduced pressure, and the residue was distilled under

reduced pressure to give 0.40 g (45%) of ethyl *N*-(*p*-methylphenyl)acetimidate, bp 102 °C (17 mmHg).

Preparation of 1b by Amide Exchange Reaction Compound **1a** (4.23 g, 0.01 mol) and the sodium salt of *N*-tosyl-*p*-chloroaniline (9.11 g, 0.03 mol) were dissolved in 100 ml of DMSO. The mixture was heated at 90 °C for 2.5 h, and concentrated under reduced pressure. The residue was washed with a small amount of ether, and $CHCl_3$ was added to the residue. The $CHCl_3$ solution was washed with 2 N NaOH, dried over K_2CO_3, and concentrated under reduced pressure. The residue was recrystallized from AcOEt to give 3.12 g (76%) of **1b**. mp 178 °C. *Anal.* Calcd for $C_{22}H_{21}ClN_2O_2S$: C, 63.99; H, 5.13; N, 6.78. Found: C, 63.90; H, 5.10; N, 6.84. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.68 (3H, s, 2-position), 2.31 (3H, s, N^2-aryl CH_3), 2.43 (3H, s, tosyl CH_3), 6.55 (2H, d, J=8 Hz, 2''- and 6''-positions), 7.08 (2H, d, J=8 Hz, 3''- and 5''-positions), 7.24 (2H, d, J=9 Hz, 3'''- and 5'''-positions), 7.26 (2H, d, J=9 Hz, 2'- and 6'-positions), 7.40 (2H, d, J=9 Hz, 3'- and 5'-positions) and 7.78 (2H, d, J=9 Hz, 2'''- and 6'''-positions).

Preparation of 1d by Beckmann Rearrangement Tosyl chloride (6.00 g, 0.033 mol) was dissolved in 40 ml of THF, and the solution was added to a solution of *p*-methoxyacetophenoxime (4.96 g, 0.03 mol) and Et_3N (3.33 g, 0.033 mol) in 40 ml of THF under ice-cooling. The mixture was kept for 1 d in an ice-box, then filtered, and the sodium salt of *N*-tosyl-*p*-nitroaniline (9.43 g, 0.03 mol) was added to the filtrate. The mixture was refluxed for 1 h, and filtered hot. The filtrate was concentrated under reduced pressure, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with 1 N NaOH, dried over K_2CO_3, and concentrated under reduced pressure. The residue was washed with a small amount of ether, and recrystallized from AcOEt to give 6.78 g (51%) of **1d**. mp 184 °C. *Anal.* Calcd for $C_{22}H_{21}N_3O_5S$: C, 60.12; H, 4.82; N, 9.56. Found: C, 60.24; H, 4.80; N, 9.51. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.81 (3H, s, 2-position), 2.44 (3H, s, tosyl CH_3), 3.79 (3H, s, OCH_3), 6.62 (2H, d, J=9 Hz, 2''- and 6''-positions), 6.85 (2H, d, J=9 Hz, 3''- and 5''-positions), 7.27 (2H, d, J=8 Hz, 3'''- and 5'''-positions), 7.52 (2H, d, J=9 Hz, 2'- and 6'-positions), 7.74 (2H, d, J=8 Hz, 2'''- and 6'''-positions) and 8.29 (2H, d, J=9 Hz, 3'- and 5'-positions).

Reaction of 1c and the Potassium Salt of *N*-(*p*-Chlorobenzoyl)-*p*-anisidine *N*-(*p*-Chlorobenzoyl)-*p*-anisidine (5.23 g, 0.02 mol) was dissolved in 145 ml of THF at 60 °C. The hot solution was added to a mixture of 3.36 g (0.03 mol) of *tert*-BuOK and 20 ml of THF with stirring. The mixture was stirred for 30 min at room temperature, and the precipitate was collected. A hot (60 °C) solution of **1c** (8.88 g, 0.02 mol) in 100 ml of THF was added to the precipitate, and the whole was allowed to stand for 1 d at room temperature. The precipitate was collected, and the filtrate was concentrated under reduced pressure. Water and $CHCl_3$ were added to the residue, and the $CHCl_3$ layer was extracted with 1 N NaOH. The aqueous layers were combined with the above precipitate, and the whole was treated as usual to give 5.12 g (88%) of *N*-tosyl-*p*-nitroaniline. The $CHCl_3$ layer was dried over K_2CO_3, and concentrated under reduced pressure. A small amount of ether was added to the residue, and the mixture was filtered with suction to give 0.28 g (5%) of recovered *N*-(*p*-chlorobenzoyl)-*p*-anisidine. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from petroleum benzin to give 3.12 g (38%) of a mixture of **2a** and **2a'**. mp 131 °C. *Anal.* Calcd for $C_{22}H_{18}Cl_2N_2O_2$: C, 63.93; H, 4.39; N, 6.78. Found: C, 64.00; H, 4.39; N, 6.84. The ^{1}H-NMR spectra of N^1-(*p*-chlorobenzoyl)-N^1,N^2-di(*p*-methoxyphenyl)acetamidine and N^1-(*p*-chlorobenzoyl)-N^1,N^2-di(*p*-chlorophenyl)acetamidine showed minor signals owing to conformational isomers besides the main signals.[3] The relative integrated intensities of the signals of the amidine central methyl group showed that the mixture consisted of two conformational isomers in a ratio of 1 : 6 in each case. ^{1}H-NMR ($CDCl_3$, 400 MHz) of the mixture of **2a** and **2a'** showed signals of OCH_3 at δ: 3.72 (1), 3.75 (5), 3.77 (6) and 3.79 (30). The relative integrated intensities are shown in parentheses. The results showed that the mixture consisted of two structural isomers in a ratio of 1 : 5. The main signals were proved to be attributable to **2a** by NOE and INDOR techniques: δ: 2.09 (s, 2-position), 6.50 (d, J=9 Hz, 2''- and 6''-positions), 6.89 (d, J=9 Hz, 3'- and 5'-positions), 7.12 (d, J=9 Hz, 2'- and 6'-positions), 7.22 (d, J=9 Hz, 3''- and 5''-positions), 7.31 (d, J=9 Hz, 3'''- and 5'''-positions) and 7.55 (d, J=9 Hz, 2'''- and 6'''-positions). The signals of **2a'** were observed at δ: 2.11 (s, 2-position), 6.81 (d, J=9 Hz, 3''- and 5''-positions), 7.16 (d, J=9 Hz, 2'- and 6'-positions) and 7.36 (d, J=9 Hz, 3'- and 5'-positions). The signals of the 2''- and 6''-, 2'''- and 6'''-, and 3'''- and 5'''-positions were probably overlapped with those of **2a**. The conclusion that the mixture consists of **2a** and **2a'** in a ratio of 5 : 1 was supported by the result of acid hydrolysis as described in the section after next.

Reaction of 1d and the Potassium Salt of *N*-(*p*-Chlorobenzoyl)-*p*-anisidine Compound **1d** (4.39 g, 0.01 mol) and *N*-(*p*-chlorobenzoyl)-*p*-chloroaniline (2.66 g, 0.01 mol) were treated in the same manner as described in the preceding section to give *N*-tosyl-*p*-nitroaniline (2.55 g, 87%) and a mixture of **2a** and **2a'** (1.28 g, 31%). mp 133 °C. The latter was identical with that obtained by the reaction of **1c** and *N*-(*p*-chlorobenzoyl)-*p*-anisidine on the basis of comparison of their IR spectra.

Acid Hydrolysis of the Mixture of 2a and 2a' The mixture of **2a** and **2a'** (0.41 g, 1 mmol) was dissolved in 10 ml of THF, and 2 ml of H_2O and 2 ml of 1 N HCl were added to the solution. The whole was kept for 2 h at room temperature, then 40 ml of 7% $NaHCO_3$ was added, and reaction mixture was distilled under reduced pressure. The distillate was treated as usual to give a trace of *p*-anisidine. Water and $CHCl_3$ were added to the residue, and the $CHCl_3$ layer was extracted with 7% $NaHCO_3$. No organic material could be detected in the $NaHCO_3$ layer. The $CHCl_3$ layer was dried over K_2CO_3, and concentrated under reduced pressure. The residue was subjected to preparative thin layer chromatography (PTLC) (silica gel with benzene : AcOEt = 4 : 1) to give 0.06 g (23%) of *N*-(*p*-chlorobenzoyl)-*p*-chloroaniline, 0.06 g (23%) of *N*-(*p*-chlorobenzoyl)-*p*-anisidine, 0.01 g (6%) of *N*-acetyl-*p*-chloroaniline and 0.01 g (6%) of *N*-acetyl-*p*-anisidine.

Reaction of 3a and *p*-Chlorobenzoyl Chloride Compound **3a** (0.57 g, 2 mmol) and Et_3N (0.30 g, 3 mmol) were dissolved in 5 ml of benzene. A solution of *p*-chlorobenzoyl chloride in 5 ml of benzene was added, and the whole was refluxed for 1 h, then filtered. The filtrate was washed with 7% $NaHCO_3$, dried over K_2CO_3, and concentrated under reduced pressure. A small amount of ether was added to the residue, and the deposited crystals were collected, and recrystallized from petroleum benzin to give 0.49 g (58%) of **2b**. mp 116 °C. *Anal.* Calcd for $C_{22}H_{18}ClN_3O_4$: C, 62.34; H, 4.28; N, 9.91. Found: C, 62.35; H, 4.24; N, 9.97. The ^{1}H-NMR ($CDCl_3$, 400 MHz at 25 °C) showed somewhat broad signals at δ: 2.17 (3H, s, 2-position), 3.79 (3H, s, OCH_3), 6.70 (2H, d, J=8 Hz, 2''- and 6''-positions), 6.88 (2H, d, J=8 Hz, 3'- and 5'-positions), 7.11 (2H, d, J=8 Hz, 2'- and 6'-positions), 7.31 (2H, d, J=8 Hz, 3'''- and 5'''-positions), 7.55 (2H, d, J=8 Hz, 2'''- and 6'''-positions) and 8.15 (2H, d, J=8 Hz, 3''- and 5''-positions).

Acid Hydrolysis of 2b Compound **2b** (0.42 g, 1 mmol) was dissolved in 10 ml of THF, then 2 ml of H_2O and 2 ml of 1 N HCl were added. The mixture was kept for 2 h at room temperature, and 40 ml of 7% $NaHCO_3$ was added. The whole was distilled under reduced pressure, and no organic material could be detected in the distillate. Water and $CHCl_3$ were added to the residue, and the $CHCl_3$ layer was extracted with 7% $NaHCO_3$. No organic material could be detected in the aqueous layer. The $CHCl_3$ layer was dried over K_2CO_3, and concentrated under reduced pressure. The residue was subjected to PTLC (silica gel with benzene : AcOEt = 6 : 1) to give 0.14 g (52%) of *N*-(*p*-chlorobenzoyl)-*p*-anisidine and 0.10 g (56%) of *N*-acetyl-*p*-nitroaniline.

Reaction of 4 and *p*-Chlorobenzoyl Chloride A solution of *p*-chlorobenzoyl chloride (2.10 g, 12 mmol) in 3 ml of benzene was added to a mixture of **4** (1.93 g, 10 mmol) and Et_3N (1.52 g, 15 mmol) and 7 ml of benzene. The whole was refluxed for 3 h, filtered hot. The filtrate was allowed to cool at room temperature, and the deposited crystals were collected to give crude **5**. Recrystallization from benzene gave 2.69 g (81%) of pure sample melting at 142 °C. *Anal.* Calcd for $C_{16}H_{14}ClN_3O_3$: C, 57.93; H, 4.25; N, 12.67. Found: C, 57.97; H, 4.36; N, 12.62. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 2.10 (3H, s, 2-position), 3.37 (3H, s, NCH_3), 6.75 (2H, d, J=9 Hz, 2''- and 6''-positions), 7.47 (2H, d, J=8 Hz, 3'''- and 5'''-positions), 7.58 (2H, d, J=8 Hz, 2'''- and 6'''-positions) and 8.18 (2H, d, J=9 Hz, 3''- and 5''-positions).

Reaction of 6a and *p*-Chlorobenzoyl Chloride Compound **6a** (2.71 g, 10 mmol) and Et_3N (1.21 g, 12 mmol) were dissolved in 15 ml of anhydrous THF. *p*-Chlorobenzoyl chloride (1.93 g, 11 mmol) was added to the solution under ice-cooling. The whole was kept for 1 h at room temperature, and filtered. The filtrate was concentrated under reduced pressure, and $CHCl_3$ was added to the residue. The $CHCl_3$ solution was washed with 7% $NaHCO_3$, dried over K_2CO_3, and concentrated under reduced pressure. A small amount of ether was added to the residue, and the ether solution was concentrated under reduced pressure. The residue was dissolved in a small amount of $CHCl_3$, and petroleum ether was added to give **7a** as a precipitate (0.05 g, 1%). mp 132 °C. *Anal.* Calcd for $C_{21}H_{16}ClN_3O_4$: C, 61.55; H, 3.94; N, 10.25. Found: C, 61.95; H, 4.09; N, 9.93. Selected ^{1}H-NMR data ($CDCl_3$, 400 MHz) are shown in Chart 4. The ether insoluble part was washed with a small amount of $CHCl_3$, and recrystallized from benzene to give 2.10 g (51%) of **7a**. mp 185 °C. *Anal.* Calcd for $C_{21}H_{16}ClN_3O_4$: C, 61.55; H, 3.94; N, 10.25. Found: C, 61.73; H, 3.91; N, 10.26. Selected ^{1}H-NMR data ($CDCl_3$, 400 MHz) are shown in Chart 4.

Acid Hydrolysis of 7a and 7b Compound **7a** (0.41 g, 1 mmol) was dissolved in 10 ml of THF, and 2 ml of H_2O and 2 ml of 1 N HCl were added to the solution. The mixture was kept for 3 h at room temperature, then 40 ml of 7% $NaHCO_3$ was added, and the whole was distilled under reduced pressure. No organic material could be detected in the distillate. Water and $CHCl_3$ were added to the residue, and the $CHCl_3$ layer was extracted with 7% $NaHCO_3$. No organic material could be detected in the $NaHCO_3$ layer. The $CHCl_3$ layer was dried over K_2CO_3, and concentrated under reduced pressure. The residue was subjected to PTLC (silica gel with benzene : AcOEt = 6 : 1) to give 0.06 g (23%) of *N*-(*p*-chlorobenzoyl)-*p*-anisidine, 0.05 g (36%) of *p*-nitroaniline and a small amount of *N*-formyl-*p*-nitroaniline.

Compound **7b** (0.08 g, 0.2 mmol) was dissolved in 5 ml of THF, and 0.5 ml of H_2O and 0.5 ml of 1 N HCl were added to the solution. The whole was kept for 2 h at room temperature, and was treated as above to give 0.03 g (56%) of *N*-(*p*-chlorobenzoyl)-*p*-nitroaniline, a small amount of *N*-formyl-*p*-anisidine and *p*-anisidine.

Reaction of 8 and *p*-Chlorobenzoyl Chloride Compound **8** (2.69 g, 10 mmol) and Et_3N (1.21 g, 12 mmol) were dissolved in 15 ml of anhydrous THF. *p*-Chlorobenzoyl chloride (1.93 g, 11 mmol) was added to the solution under ice-cooling. The mixture was stirred for 2 h under ice-cooling, then filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$, and the solution was washed with 7% $NaHCO_3$, dried over K_2CO_3, and concentrated under reduced pressure. The residue was dissolved in 10 ml of $CHCl_3$ at 50 °C, and the solution was allowed to cool to room temperature. The precipitate was collected, and dissolved in $CHCl_3$, and ether was added to the solution. The precipitate was collected to give 1.63 g (40%) of **9b**. mp 146 °C. *Anal.* Calcd for $C_{22}H_{18}ClN_3O_3$: C, 64.79; H, 4.45; N, 10.30. Found: C, 64.84; H, 4.39; N, 10.34. Selected ^{1}H-NMR data ($CDCl_3$, 400 MHz) are shown in Chart 5. The $CHCl_3$ soluble part was concentrated under reduced pressure, and a small amount of ether was added to the residue. The precipitate was collected, and recrystallized from petroleum benzin to give 1.20 g (29%) of **9a**. mp 130 °C. *Anal.* Calcd for $C_{22}H_{18}ClN_3O_3$: C, 64.79; H, 4.45; N, 10.30. Found: C, 64.95; H, 4.46; N, 10.18. Selected ^{1}H-NMR data ($CDCl_3$, 400 MHz) are shown in Chart 5.

Compound **9a** was recovered unchanged on refluxing its benzene solution for 9 h. Compound **9b** (0.20 g, 0.5 mmol) was dissolved in 3 ml of benzene, and the solution was refluxed for 9 h. The mixture was concentrated under reduced pressure, and the residue was recrystallized from petroleum benzin to give 0.12 g (60%) of **9a**.

Acid Hydrolysis of 9a and 9b Compound **9a** (0.20 g, 0.5 mmol) was dissolved in 3 ml of THF, and 1 ml of 1 N HCl was added to the solution. The mixture was kept for 2 h at room temperature, then 10 ml of 7% $NaHCO_3$ was added, and the whole was concentrated under reduced pressure. Ether and H_2O were added to the residue. No organic material could be detected in the aqueous layer. The ether layer was dried over K_2CO_3, and concentrated under reduced pressure. The residue was subjected to PTLC (silica gel with benzene : AcOEt = 6 : 1) to give *p*-nitroaniline (0.06 g, 87%), *N*-(*p*-chlorobenzoyl)-*p*-methylbenzylamine (0.01 g, 8%) and *N*-formyl-*N*-(*p*-chlorobenzoyl)-*p*-methylbenzylamine (petroleum benzin, 0.07 g, 49%). mp 99 °C. *Anal.* Calcd for $C_{16}H_{14}ClNO_2$: C, 66.79; H, 4.90; N, 4.87. Found: C, 66.81; H, 4.93; N, 4.98. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 2.33 (3H, s, CH_3), 5.00 (2H, s, CH_2), 7.10 and 7.28 (each 2H, d, J=9 Hz, 2-, 6- and 3-, 5-positions of $CH_3C_6H_4$), 7.42 (4H, s, 2-, 6- and 3-, 5-positions of ClC_6H_4) and 8.92 (1H, s, CHO).

Compound **9b** (0.20 g, 0.5 mmol) was dissolved in 3 ml of THF, and 1 ml of 1 N HCl was added to the solution. The mixture was kept for 2 h at room temperature, then 10 ml of 7% $NaHCO_3$ was added, and the precipitate was collected to give 0.11 g (90%) of *N*-(*p*-chlorobenzoyl)-*p*-nitroaniline. Ether was added to the filtrate. No organic material could be detected in the aqueous layer. The ether layer was dried over K_2CO_3, and concentrated under reduced pressure. The residue was recrystallized from petroleum benzin to give 0.05 g (67%) of *N*-formyl-*p*-methylbenzylamine.

Preparation of 1f by Amide Exchange Reaction Compound **1e** (4.56 g, 0.01 mol) and the sodium salt of *N*-tosyl-*p*-chloroaniline (3.04 g, 0.01 mol) were dissolved in 150 ml of DMF under heating at 90 °C. The whole was heated at 90 °C for 3 h, then concentrated under reduced pressure, and $CHCl_3$ and 1 N NaOH were added to the residue. The $CHCl_3$ layer was washed with 1 N NaOH, dried over K_2CO_3, and concentrated under reduced pressure. The residue was washed with a small amount of ether, and recrystallized from AcOEt to give 2.76 g (62%) of **1f**. mp 205 °C. *Anal.* Calcd for $C_{21}H_{18}ClN_3O_4S$: C, 56.82; H, 4.09; N, 9.47. Found: C, 56.81; H, 4.06; N, 9.60. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.73 (3H, s, 2-position), 2.50 (3H, s, tosyl CH_3), 6.70 (2H, d, J=9 Hz, 2''- and 6''-positions), 7.17—7.50 (6H, m, aryl H), 7.80 (2H, d, J=8 Hz, 2'''- and 6'''-positions) and 8.07 (2H, d, J=9 Hz, 3''- and 5''-positions).

Alcoholysis of 1f Compound **1f** (2.22 g, 5 mmol) was dissolved in 60 ml of anhydrous THF. Anhydrous EtOH (110 ml) and NaOEt solution (prepared from 0.46 g of sodium and 25 ml of anhydrous EtOH) were added, and the whole was allowed to stand for 1 d at room temperature, then saturated with CO_2. The mixture was concentrated under reduced pressure, and ether and 2 N NaOH were added to the residue. The NaOH layer was treated as usual to give 0.84 g (60%) of *N*-tosyl-*p*-chloroaniline. The ether layer was dried over K_2CO_3, and concentrated under reduced pressure. The residue was distilled under reduced pressure to give 0.65 g (63%) of ethyl *N*-(*p*-nitrophenyl)acetimidate. bp 180 °C (19 mmHg). mp 63 °C.

Preparation of 1g by Amide Exchange Reaction Compound **1e** (4.54 g, 0.01 mol) and the sodium salt of *N*-tosyl-*p*-toluidine (2.83 g, 0.01 mol) were dissolved in 160 ml of DMF. The solution was heated at 90 °C for 2 h, and concentrated under reduced pressure. Water and $CHCl_3$ were added to the residue, and the $CHCl_3$ layer was washed with 1 N NaOH, dried over K_2CO_3, and concentrated under reduced pressure. The residue was recrystallized from AcOEt to give 2.26 g (53%) of **1g**. mp 217 °C. *Anal.* Calcd for $C_{22}H_{21}N_3O_4S$: C, 62.40; H, 5.00; N, 9.92. Found: C, 62.62; H, 4.99; N, 9.99. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.65 (3H, s, 2-position), 2.42 (3H, s, tolyl CH_3), 2.46 (3H, s, tosyl CH_3), 6.71 (2H, d, J=9 Hz, 2''- and 6''-positions), 7.22 (2H, d, J=8 Hz, 2'- and 6'-positions), 7.28 (2H, d, J=8 Hz, 3'- and 5'-positions), 7.29 (2H, d, J=8 Hz, 3'''- and 5'''-positions), 7.82 (2H, d, J=8 Hz, 2'''- and 6'''-positions) and 8.15 (2H, d, J=9 Hz, 3''- and 5''-positions).

Preparation of *m*-Nitroacetophenoxime Tosylate Tosyl chloride (15.24 g, 0.08 mol) was added to a solution of *m*-nitroacetophenoxime (14.40 g, 0.08 mol) and Et_3N (9.70 g, 0.096 mol) in 80 ml of benzene. The whole was allowed to stand for 1 d at room temperature. The mixture was filtered, and the filtrate was washed with 7% $NaHCO_3$, dried over K_2CO_3, and concentrated under reduced pressure. The residue was recrystallized from benzene to give 18.55 g (69%) of *m*-nitroacetophenoxime tosylate. mp 115 °C. *Anal.* Calcd for $C_{14}H_{14}N_2O_5S$: C, 53.88; H, 4.22; N, 8.38. Found: C, 53.69; H, 4.19; N, 8.28. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 2.40 (3H, s, CH_3), 2.45 (3H, s, tosyl CH_3), 7.34 (2H, d, J=9 Hz, 3''- and 5''-positions), 7.57 (1H, d, J=8 Hz, 5'-position), 7.95 (3H, d, J=9 Hz, 2''-, 6''- and 6'-positions), 8.30 (1H, ddd, J=1, 2, 8 Hz, 4'-position) and 8.42 (1H, t, J=2 Hz, 2'-position).

Beckmann Rearrangement of *m*-Nitroacetophenoxime Tosylate in the Presence of the Sodium Salt of *N*-Tosyl-*p*-nitroaniline A mixture of *m*-nitroacetophenoxime tosylate (1.11 g, 3 mmol), the sodium salt of *N*-tosyl-*p*-nitroaniline (1.05 g, 3 mmol) and 30 ml of anisole was refluxed with stirring for 5 h on an oil bath (190 °C). The hot mixture was filtered with suction, and the precipitate was washed successively with H_2O, 1 N NaOH and H_2O, and recrystallized from DMF to give 0.70 g (51%) of **1i**. The filtrate (anisole soluble part) was washed with 1 N NaOH, dried over K_2CO_3, and concentrated under reduced pressure. The residue was washed with a small amount of ether, and recrystallized from AcOEt to give 0.46 g (34%) of **1h**. Compound **1i**, mp 220 °C. *Anal.* Calcd for $C_{21}H_{18}N_4O_6S$: C, 55.50; H, 3.99; N, 12.33. Found: C, 55.39; H, 3.94; N, 12.34. ^{1}H-NMR (DMSO-d_6, 400 MHz) 1.71 (3H, s, 2-position), 2.45 (3H, s, tosyl CH_3), 6.81 (2H, d, J=9 Hz, 2''- and 6''-positions), 7.47 (2H, d, J=8 Hz, 3'''- and 5'''-positions), 7.83 (2H, d, J=8 Hz, 2'''- and 6'''-positions), 7.84 (1H, t, J=8 Hz, 5'-position), 7.96 (1H, ddd, J=1, 2, 8 Hz, 6'-position), 8.18 (2H, d, J=9 Hz, 3''- and 5''-positions), 8.31 (1H, t, J=2 Hz, 2'-position) and 8.39 (1H, ddd, J=1, 2, 8 Hz, 4'-position). Compound **1h**, mp 194 °C. *Anal.* Calcd for $C_{21}H_{18}N_4O_6S$: C, 55.50; H, 3.99; N, 12.33. Found: C, 55.38; H, 3.94; N, 12.23. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 1.70 (3H, s, 2-position), 2.45 (3H, s, tosyl CH_3), 7.07 (1H, ddd, J=1, 2, 8 Hz, 6''-position), 7.36 (1H, t, J=2 Hz, 2''-position), 7.46 (2H, d, J=8 Hz, 3'''- and 5'''-positions), 7.57 (1H, t, J=8 Hz, 5''-position), 7.81 (2H, d, J=9 Hz, 2'- and 6'-positions), 7.82 (2H, d, J=8 Hz, 2'''- and 6'''-positions), 7.90 (1H, ddd, J=1, 2, 8 Hz, 4''-position) and 8.38 (2H, d, J=9 Hz, 3'- and 5'-positions).

Alcoholysis of 1h and 1i Compound **1h** (2.27 g, 5 mmol) was treated in the same manner as described for the alcoholysis of **1f** to give 0.57 g (55%) of ethyl *N*-(*m*-nitrophenyl)acetimidate and 1.08 g (74%) of *N*-tosyl-*p*-nitroaniline. Similar treatment of **1i** (2.27 g, 5 mmol) gave 0.81 g (78%) of ethyl *N*-(*p*-nitrophenyl)acetimidate and 1.13 g (77%) of *N*-tosyl-*m*-nitroaniline.

Preparation of 1h by Beckmann Rearrangement *m*-Nitroacetophenoxime tosylate (3.34 g, 0.01 mol) and the sodium salt of *N*-tosyl-*p*-nitroaniline (3.14 g, 0.01 mol) were dissolved in 20 ml of DMF. The whole was

heated at 90 °C for 2 h, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$, and the solution was washed with 1 N NaOH, dried over K_2CO_3, and concentrated under reduced pressure. The residue was washed with a small amount of ether, and recrystallized from AcOEt to give 1.75 g (39%) of **1h**.

Preparation of 1i by Beckmann Rearrangement A mixture of *p*-nitroacetophenoxime tosylate (3.34 g, 0.01 mol), the sodium salt of *N*-tosyl-*m*-nitroaniline (3.14 g, 0.01 mol) and 70 ml of xylene was refluxed for 5.5 h. The hot mixture was filtered with suction. The precipitate was washed successively with H_2O, 1 N NaOH and H_2O, and recrystallized from DMF to give 1.97 g (49%) of **1i**.

Conversion of 1a into 1g by Tosyl Migration A solution of **1a** (0.50 g, 1.2 mmol) in 50 ml of xylene was refluxed for 20 h. The mixture was washed with 1 N NaOH, dried over K_2CO_3, and concentrated under reduced pressure. The residue was recrystallized from AcOEt to give 0.24 g (48%) of **1g**.

Preparation of 1l by Amide Exchange Reaction A solution of **1e** (6.81 g, 15 mmol) and the sodium salt of *N*-tosylmethylamine (3.11 g, 15 mmol) in 250 ml of DMF was heated at 90 °C for 1.5 h. The mixture was concentrated under reduced pressure. Water and $CHCl_3$ were added to the residue, and the $CHCl_3$ layer was washed with 1 N NaOH, dried over K_2CO_3, and concentrated under reduced pressure. The residue was washed with a small amount of ether, and recrystallized from AcOEt to give 3.76 g (76%) of **1l**. mp 165 °C. *Anal.* Calcd for $C_{16}H_{17}N_3O_4S$: C, 55.32; H, 4.93; N, 12.10. Found: C, 55.38; H, 4.93; N, 12.02. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.16 (3H, s, 2-position), 2.47 (3H, s, tosyl CH_3), 3.38 (3H, s, N–CH_3), 6.70 (2H, d, J=9 Hz, 2″- and 6″-positions), 7.39 (2H, d, J=8 Hz, 3‴- and 5‴-positions), 7.76 (2H, d, J=8 Hz, 2‴- and 6‴-positions) and 8.16 (2H, d, J=9 Hz, 3″- and 5″-positions).

Alcoholysis of 1l Compound **1l** (1.74 g, 5 mmol) was treated in the same manner as described for the alcoholysis of **1f** to give 0.79 g (76%) of ethyl *N*-(*p*-nitrophenyl)acetimidate and 0.65 g (71%) of *N*-tosylmethylamine.

Beckmann Rearrangement of Acetoxime Tosylate in the Presence of the Sodium Salt of *N*-Tosyl-*p*-nitroaniline A mixture of acetoxime tosylate (1.14 g, 5 mmol), the sodium salt of *N*-tosyl-*p*-nitroaniline (1.57 g, 5 mmol) and 20 ml of xylene was refluxed for 8 h. The mixture was filtered hot, and the filtrate was washed with 10% Na_2CO_3, dried over K_2CO_3, and concentrated under reduced pressure. The residue was washed with a small amount of ether, and recrystallized from AcOEt to give 1.02 g (59%) of **1l**. The sample was identical with that prepared by the reaction of **1e** and the sodium salt of *N*-tosylmethylamine on the basis of mixed melting point measurement and comparison of their IR spectra.

Preparation of 2c by Amide Exchange Reaction A solution of *N*-(*p*-chlorobenzoyl)-*p*-anisidine (1.31 g, 5 mmol) in 40 ml of anhydrous THF was added to a mixture of *tert*-BuOK (0.84 g, 7.5 mmol) and 3 ml of anhydrous THF with stirring. A solution of **1h** (2.62 g, 5.5 mmol) in 50 ml of anhydrous THF was added to the mixture with stirring. The whole was allowed to stand for 1 d, and filtered. The filtrate was saturated with CO_2, and concentrated under reduced pressure. Water and $CHCl_3$ were added to the residue, and the $CHCl_3$ layer was washed with 1 N NaOH, dried over K_2CO_3, and concentrated under reduced pressure. Ether was added to the residue, and the ether-insoluble part was collected, and recrystallized from petroleum benzin to give 1.40 g (68%) of **2c**. mp 113 °C. *Anal.* Calcd for $C_{22}H_{18}ClN_3O_4$: C, 62.34; H, 4.28; N, 9.91. Found: C, 62.31; H, 4.22; N, 9.84. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.17 (3H, s, 2-position), 3.80 (3H, s, OCH_3), 6.89 (2H, d, J=9 Hz, 3′- and 5′-positions), 6.92 (1H, ddd, J=1, 2, 8 Hz, 6″-position), 7.13 (2H, d, J=9 Hz, 2′- and 6′-positions), 7.32 (2H, d, J=9 Hz, 3‴- and 5‴-positions), 7.43 (1H, t, J=8 Hz, 5′-position), 7.46 (1H, t, J=2 Hz, 2″-position), 7.56 (2H, d, J=9 Hz, 2‴- and 6‴-positions) and 7.90 (1H, ddd, J=1, 2, 8 Hz, 4″-position). Other small signals owing to conformational isomer were observed.

Preparation of 2d by Amide Exchange Reaction *N*-(*p*-Chlorobenzoyl)-*p*-toluidine (1.23 g, 5 mmol) and **1h** were treated in the same manner as described in the preceding section to give 0.75 g (37%) of **2d**. mp 112 °C (petroleum benzin). *Anal.* Calcd for $C_{22}H_{18}ClN_3O_3$: C, 64.79; H, 4.45; N, 10.30. Found: C, 65.00; H, 4.52; N, 10.02. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.17 (3H, s, 2-position), 2.34 (3H, s, tolyl CH_3), 6.92 (1H, ddd, J=1, 2, 8 Hz, 6″-position), 7.09 (2H, d, J=8 Hz, 2′- and 6′-positions), 7.19 (2H, d, J=8 Hz, 3′- and 5′-positions), 7.32 (2H, d, J=9 Hz, 3‴- and 5‴-positions), 7.43 (1H, t, J=8 Hz, 5″-position), 7.46 (1H, t, J=2 Hz, 2″-position), 7.57 (2H, d, J=9 Hz, 2‴- and 6‴-positions) and 7.90 (1H, ddd, J=1, 2, 8 Hz, 4″-position). Other small signals owing to a conformational isomer were observed.

Alcoholysis of 2c Compound **2c** (0.82 g, 2 mmol) was dissolved in 5 ml of anhydrous THF, then 10 ml of anhydrous EtOH and 1 ml of 0.5 N NaOEt in EtOH were added. The whole was allowed to stand for 1 d at room temperature, and saturated with CO_2. The mixture was concentrated under reduced pressure, and water and ether were added to the residue. Then 5 ml of 2 N HCl was added to the ether layer with stirring, and the precipitate (HCl salt of **3c**) was collected and treated as usual to give 0.51 g (89%) of **3c**. mp 147 °C (benzene). *Anal.* Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.70. Found: C, 63.13; H, 5.30; N, 14.74. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.97 (3H, s, 2-position), 3.75 (3H, s, OCH_3), 6.80 (2H, d, J=9 Hz, 3′- and 5′-positions), 7.00—7.50 (4H, m, aryl H) and 7.77 (2H, m, 2″- and 4″-positions). The filtrate (ether solution) was washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was distilled under reduced pressure to give 0.25 g (68%) of ethyl *p*-chlorobenzoate.

Alcoholysis of 2d Compound **2d** (0.41 g, 1 mmol) was treated in a similar manner to that described in the preceding section to give 0.12 g (65%) of ethyl *p*-chlorobenzoate and 0.22 g (82%) of **3d**. mp 126 °C (benzene, lit.,[8] mp 134 °C). *Anal.* Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.76; H, 5.62; N, 15.46. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.95 (3H, s, 2-position), 2.30 (3H, s, tolyl CH_3), 7.17 and 7.30 (each 2H, d, J=9 Hz, 2′-, 6′- and 3′-, 5′-positions), 7.43 (2H, m, 5″- and 6″-positions) and 7.92 (2H, m, 2″- and 4″-positions).

Alkaline Hydrolysis of 2d Compound **2d** (0.41 g, 1 mmol) was dissolved in 3.5 ml of THF, and 0.5 ml of H_2O and 1 ml of 1 N NaOH were added. The mixture was stirred for 2 d at room temperature, then 7% $NaHCO_3$ and ether were added. The aqueous layer was treated as usual to give 0.13 g (84%) of *p*-chlorobenzoic acid. The ether layer was extracted with 2 N HCl, and the HCl layer was treated as usual to give 0.22 g (82%) of **3d**.

Preparation of 3c, 3d and 3e from 1h and *N*-(*p*-Chlorobenzoyl)arylamine by One-Pot Procedure A solution of *N*-(*p*-chlorobenzoyl)-*p*-anisidine (2.62 g, 12 mmol) in 60 ml of anhydrous THF was added to a mixture of *tert*-BuOK (1.34 g, 12 mmol) and 5 ml of anhydrous THF. A solution of **1h** (4.54 g, 10 mmol) in 50 ml of anhydrous THF was then added, and the whole was allowed to stand for 1 d at room temperature, then saturated with CO_2. The mixture was filtered, and the filtrate was concentrated under reduced pressure. Water and $CHCl_3$ were added to the residue, and the $CHCl_3$ layer was washed with 1 N NaOH, dried over K_2CO_3, and concentrated under reduced pressure. A small amount of $CHCl_3$ was added to the residue. The precipitate [a small amount of *N*-(*p*-chlorobenzoyl)-*p*-anisidine] was filtered off, and the filtrate was concentrated under reduced pressure. Then 2 ml of anhydrous THF, 20 ml of anhydrous EtOH and 2 ml of 1 N NaOEt in EtOH were added to the residue. The whole was allowed to stand for 1 d at room temperature, and saturated with CO_2. The mixture was filtered, and the filtrate was concentrated under reduced pressure. Water and ether were added to the residue, and then 10 ml of 2 N HCl was added to the ether solution under ice-cooling with stirring. The precipitate (HCl salt of **3c**) was collected, and treated as usual to give 1.32 g (46%) of **3c**. The ether layer of the filtrate was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was distilled under reduced pressure to give 0.94 g (51%) of ethyl *p*-chlorobenzoate.

Compound **1h** (4.54 g, 10 mmol) and *N*-(*p*-chlorobenzoyl)-*p*-toluidine (2.46 g, 10 mmol) were treated in the same manner as described above to give 1.56 g (58%) of **3d** and 0.94 g (51%) of ethyl *p*-chlorobenzoate.

Compound **1h** (4.54 g, 10 mmol) and *N*-(*p*-chlorobenzoyl)-*o*-toluidine (2.46 g, 10 mmol) were treated in the same manner as described above to give 0.91 g (49%) of ethyl *p*-chlorobenzoate and 1.69 g (63%) of **3e**. mp 124 °C (benzene). *Anal.* Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.67; H, 5.59; N, 15.72. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.92 (3H, s, 2-position), 2.22 (3H, s, tolyl CH_3), 7.00—7.58 (6H, m, aryl H), 7.78 (1H, dt, J=8, 2 Hz, 4″-position) and 8.10 (1H, t, J=2 Hz, 2″-position).

Hydrolysis of 3c, 3d and 3e in the Presence of AcOH Compound **3c** (0.57 g, 2 mmol) was dissolved in a mixture of 0.06 g of AcOH, 1.9 ml of H_2O and 2.5 ml of THF. The mixture was refluxed for 5 h, and 10 ml of 10% Na_2CO_3 and 5 ml of ether were added. The ether layer was dried over K_2CO_3, and concentrated under reduced pressure. A small amount of ether was added to the residue, and the insoluble part was collected to give 0.23 g (64%) of *N*-acetyl-*m*-nitroaniline. The ether layer was extracted with 2 N HCl, and the HCl layer was treated as usual to give 0.11 g (45%) of *p*-anisidine. The ether layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to PTLC (silica gel with benzene : AcOEt = 4 : 1) to give 0.01 g (3%) of *N*-acetyl-*p*-anisidine.

Compound **3d** (0.54 g, 2 mmol) was treated in the same manner as described above to give 0.22 g (61%) of *N*-acetyl-*m*-nitroaniline, 0.10 g

(47%) of *p*-toluidine and 0.04 g (13%) of *N*-acetyl-*p*-toluidine.

Compound **3e** (0.54 g, 2 mmol) was treated in the same manner as described above (10 h reflux) to give 0.17 g (47%) of *N*-acetyl-*m*-nitroaniline, 0.10 g (47%) of *o*-toluidine, 0.04 g (13%) of *N*-acetyl-*o*-toluidine and 0.06 g (11%) of **3e**.

One-Pot Alcoholysis of *N*-(*p*-Chlorobenzoyl)-*p*-toluidine A solution of *N*-(*p*-chlorobenzoyl)-*p*-toluidine (2.46 g, 10 mmol) in 60 ml of anhydrous THF was added to a mixture of *tert*-BuOK (1.79 g, 16 mmol) and 5 ml of anhydrous THF, then a solution of **1h** (5.45 g, 12 mmol) in 80 ml of anhydrous THF was added. The whole was allowed to stand for 2 d at room temperature, and saturated with CO_2. The mixture was concentrated under reduced pressure, and $CHCl_3$ and 1 N NaOH were added. The aqueous layer was treated as usual to give 2.95 g (84%) of *N*-tosyl-*p*-nitroaniline. The $CHCl_3$ layer was dried over K_2CO_3, and concentrated under reduced pressure. A small amount of $CHCl_3$ was added to the residue, and the insoluble part was collected to give 0.39 g (16%) of recovered amide. The $CHCl_3$ layer was concentrated under reduced pressure, and a mixture of 2 ml of 1 N NaOEt in EtOH, 20 ml of anhydrous EtOH and 2 ml of anhydrous THF was added to the residue. The whole was allowed to stand for 1 d, and then saturated with CO_2. The mixture was filtered, and the filtrate was concentrated under reduced pressure. Water and ether were added to the residue, and 10 ml of 2 N HCl was added to the ether layer with stirring under ice-cooling. The precipitate (HCl salt of **3d**) was collected, and treated as usual to give 1.68 g (63%) of crude **3d**. The ether layer was washed with 7% $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was treated as usual to give 1.05 g (57%) of ethyl *p*-chlorobenzoate. The crude **3d** was dissolved in 18 ml of THF, and 14.5 ml of H_2O and 4.5 g of AcOH were added to the solution. The mixture was refluxed for 6 h, and a solution of 7 g of Na_2CO_3 in 10 ml of H_2O was added. The whole was extracted with ether, and the ether layer was dried over K_2CO_3, and concentrated under reduced pressure. A small amount of ether was added to the residue, and the insoluble part was collected to give 0.60 g (33%) of *N*-acetyl-*m*-nitroaniline. The ether layer was concentrated under reduced pressure. The residue was distilled under reduced pressure to give 0.23 g (22%) of *p*-toluidine.

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