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Hydrolysis of Acyl Derivatives of Malonaldehyde Dianil. III[1]

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The reaction sequence of hydrolysis of *N*-acyl derivatives of malonaldehyde dianil was examined. Hydrochloric acid-catalyzed hydrolysis occurred at the imino group to form arylamine and β-(*N*-acylarylamino)acrolein; the latter compound is not stable in acidic solution. In the case of 1-(*N*-phenylcarbamoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene, hydrolysis occurred at both the imino and carbamoyl groups.

Buffer-catalyzed hydrolysis occurred at the imino group, and the resulting β-(*N*-acylarylamino)acrolein and arylamine reacted to form β-arylaminoacrolein and *N*-acylarylamine. This aminolysis reaction was suppressed in hydrochloric acid-catalyzed hydrolysis.

Alkaline hydrolysis of *N*-acyl derivatives of malonaldehyde dianil and of β-arylaminoacrolein occurred at the amide carbonyl group except in the case of 1-(*N*-tosyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene. *N*-Tosyl-*p*-toluidine was obtained in this case.

Keywords——hydrolysis; malonaldehyde dianil; β-arylaminoacrolein; 1-(*N*-acylarylamino)-3-arylimino-1-propene; β-(*N*-acylarylamino)acrolein; 1-(*N*-tosyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene; 1-(*N*-tosyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-butene; β-(*N*-tosyl-*p*-toluidino)acrolein; 4-(*N*-tosyl-*p*-toluidino)-3-buten-2-one

In the previous paper[2] we reported a kinetic study of the cyclodehydration of β-(*p*-toluidino)acrolein (I) and 4-(*p*-toluidino)-3-penten-2-one in sulfuric acid to give 6-methylquinoline and 2,4,6-trimethylquinoline. The reaction of the latter compound proceeded much faster than that of the former compound. We were next interested in the behavior of β-(*p*-toluidino)crotonaldehyde (II) in the same reaction.

1-Arylamino-3-arylimino-1-propene (malonaldehyde dianil) was hydrolyzed in aqueous ethanol to give β-arylaminoacrolein in the presence of acetic acid and sodium acetate.[3] The hydrolysis of 1-(*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-butene (III), however, did not give II but yielded 4-(*p*-toluidino)-3-buten-2-one (IV) under the same conditions.[4]

Hydrolysis of 1-(*N*-benzoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (V) gave I and *N*-benzoyl-*p*-toluidine in the presence of acetic acid and sodium acetate. Hydrolysis of 1-(*N*-benzoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-butene (VI), however, did not give II but yielded IV, 4-(*N*-benzoyl-*p*-toluidino)-3-buten-2-one (VII) and *N*-benzoyl-*p*-toluidine under the same conditions.[4] The sequence of hydrolysis of V was elucidated to be as follows: hydrolysis of V occurs at the 3-position to give β-(*N*-benzoyl-*p*-toluidino)-acrolein (VIII) and *p*-toluidine, and in the next step, aminolysis of VIII occurs at the β-position to give I and *N*-benzoyl-*p*-toluidine[1,4] (Chart 1).

p-Toluidine, 1-(*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (malonaldehyde dianil of *p*-toluidine) (IX), *N*-benzoyl-*p*-toluidine and a small amount of VIII were obtained when a solution of V in a mixture of dioxane and 1 N hydrochloric acid was allowed to stand for 10 min at room temperature. The ^{1}H nuclear magnetic resonance (^{1}H-NMR) spectrum of a solution of V in deuterium oxide–dioxane-d_8 containing deuterium chloride showed signals of the deuterium chloride salt of V at δ 6.38 (2-position, double doublet, J=11, 13 Hz), 9.03 (1-position, doublet, J=13 Hz), 9.28 (3-position, doublet, J=11 Hz) and signals of VIII at 5.23 (α-position, double doublet, J=8, 14 Hz), 8.53 (β-position, doublet, J=14 Hz) and 9.50 (aldehyde, doublet, J=8 Hz) immediately after dissolution. The intensities of

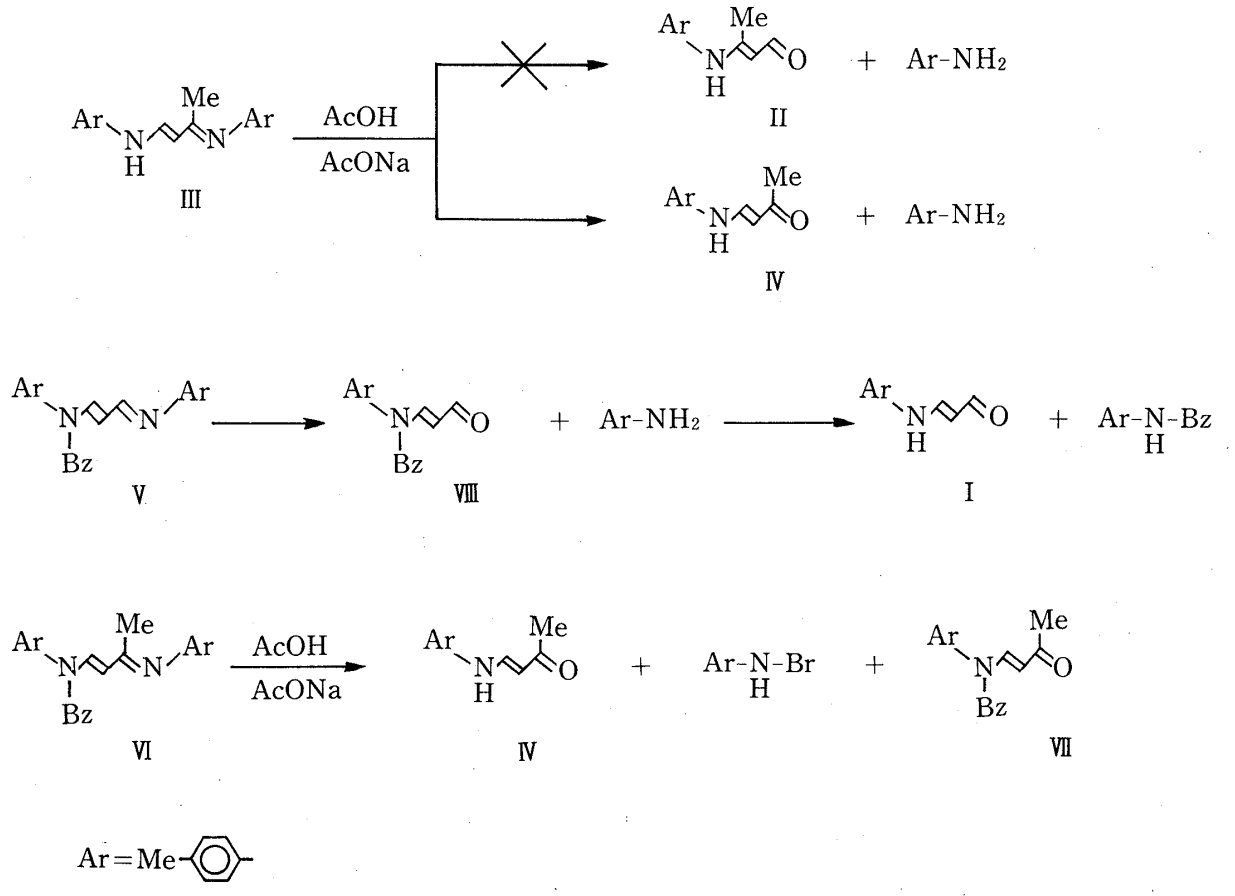


Chart 1

these signals diminished on standing,[5] and after one day all the signals due to V and VIII disappeared, suggesting that VIII is not stable in the solution containing hydrochloric acid. The ^{1}H-NMR spectrum of VIII in deuterium oxide–dioxane-d_8 containing some methanol-d_4 and deuterium chloride changed on standing, and after one day signals due to VIII had disappeared and the spectrum showed a pattern similar to that of *N*-benzoyl-*p*-toluidine. The procedure for the hydrochloric acid-catalyzed hydrolysis of V was changed as follows: a solution of V in tetrahydrofuran was added to 0.1 N hydrochloric acid with stirring, then ether was added and the mixture was stirred for an appropriate period (method A). Compound VIII, *p*-toluidine and small amounts of IX and *N*-benzoyl-*p*-toluidine were obtained when V was treated by method A (for 16 min at room temperature). Compound I, a main product of the buffer-catalyzed hydrolysis of V,[4] could not be detected in the reaction mixture. Presumably the aminolysis of VIII is suppressed, since most of the *p*-toluidine is converted into unreactive conjugate acid owing to the high acidity of the reaction solution, and malonaldehyde formed from VIII combines with *p*-toluidine to form IX. β-(*N*-Acetyl-*p*-toluidino)-acrolein (XI), *p*-toluidine and IX were obtained when 1-(*N*-acetyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (X) was treated by method A (for 15 min at room temperature). 1-(*N*-Tosyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (XIV) was prepared by the reaction of IX and *p*-toluenesulfonyl chloride in the presence of triethylamine. β-(*N*-Tosyl-*p*-toluidino)acrolein (XV), *N*-tosyl-*p*-toluidine, IX and *p*-toluidine were obtained when XIV was treated by method A (for 135 min at room temperature)(Chart 2).

β-(*N*-Phenylcarbamoyl-*p*-toluidino)acrolein (XIII), *p*-toluidine, IX, *N*,*N*′-diphenylurea and *N*-phenyl-*N*′-(*p*-methylphenyl)urea were obtained when 1-(*N*-phenylcarbamoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (XII) was treated by method A (for 10 min at room temperature). This result suggests that hydrolysis at the carbamoyl

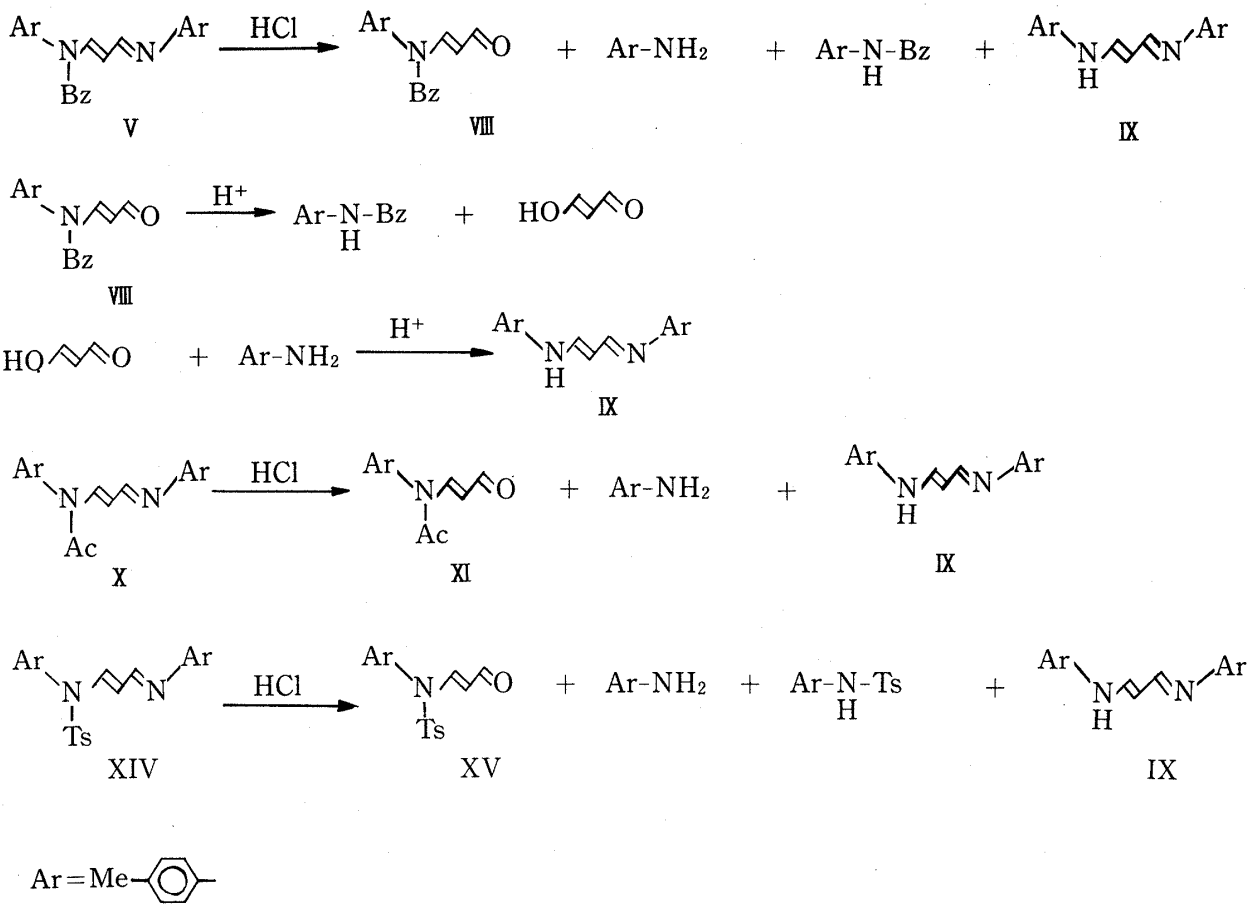


Chart 2

group to form aniline and IX proceeds in parallel with the hydrolysis at the 3-position to form *p*-toluidine and XIII, and aminolysis reactions of XII proceed successively with the amines formed (Chart 3). It has already been pointed out that the aminolysis of XII proceeds readily.[1] 1-(*N*-Benzoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-butene (VI) is less reactive than V with respect to hydrochloric acid-catalyzed hydrolysis. One-half of the starting material was recovered when VI was treated by method A for 15 min at room temperature. After stirring of the reaction mixture for 60 min, 4-(*N*-benzoyl-*p*-toluidino)-3-buten-2-one (VII), *p*-toluidine and a small amount of *N*-benzoyl-*p*-toluidine were obtained. 1-(*N*-Tosyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-butene (XVI) was prepared by the reaction of the hydrochloride of III and *p*-toluenesulfonyl chloride in the presence of triethylamine. 4-(*N*-Tosyl-*p*-toluidino)-3-buten-2-one (XVII) and *N*-tosyl-*p*-toluidine were obtained when XVI was treated by method A (for 65 min at room temperature) (Chart 4).

The hydrochloric acid-catalyzed hydrolysis of 1-(*N*-acylarylamino)-3-arylimino-1-propene occurred at the 3-position to form arylamine and β-(*N*-acylarylamino)acrolein, and no evidence for hydrolysis at the amide carbonyl group could be obtained except in the case of XII, since no substance soluble in aqueous sodium hydrogen carbonate solution could be detected in the reaction mixture in all cases of hydrochloric acid-catalyzed hydrolysis. No evidence for aminolysis at the β-position of β-(*N*-acylarylamino)acrolein could be obtained either. From the above observations, it may be expected that the preparation of 3-(*N*-acylarylamino)-1-arylimino-2-butene would lead to the synthesis of β-arylaminocrotonaldehydes.

As reported previously,[4] *N*-acetyl-*p*-toluidine, XI, I and IX were obtained when a solution of X in aqueous dioxane containing equimolar amounts of acetic acid and sodium acetate

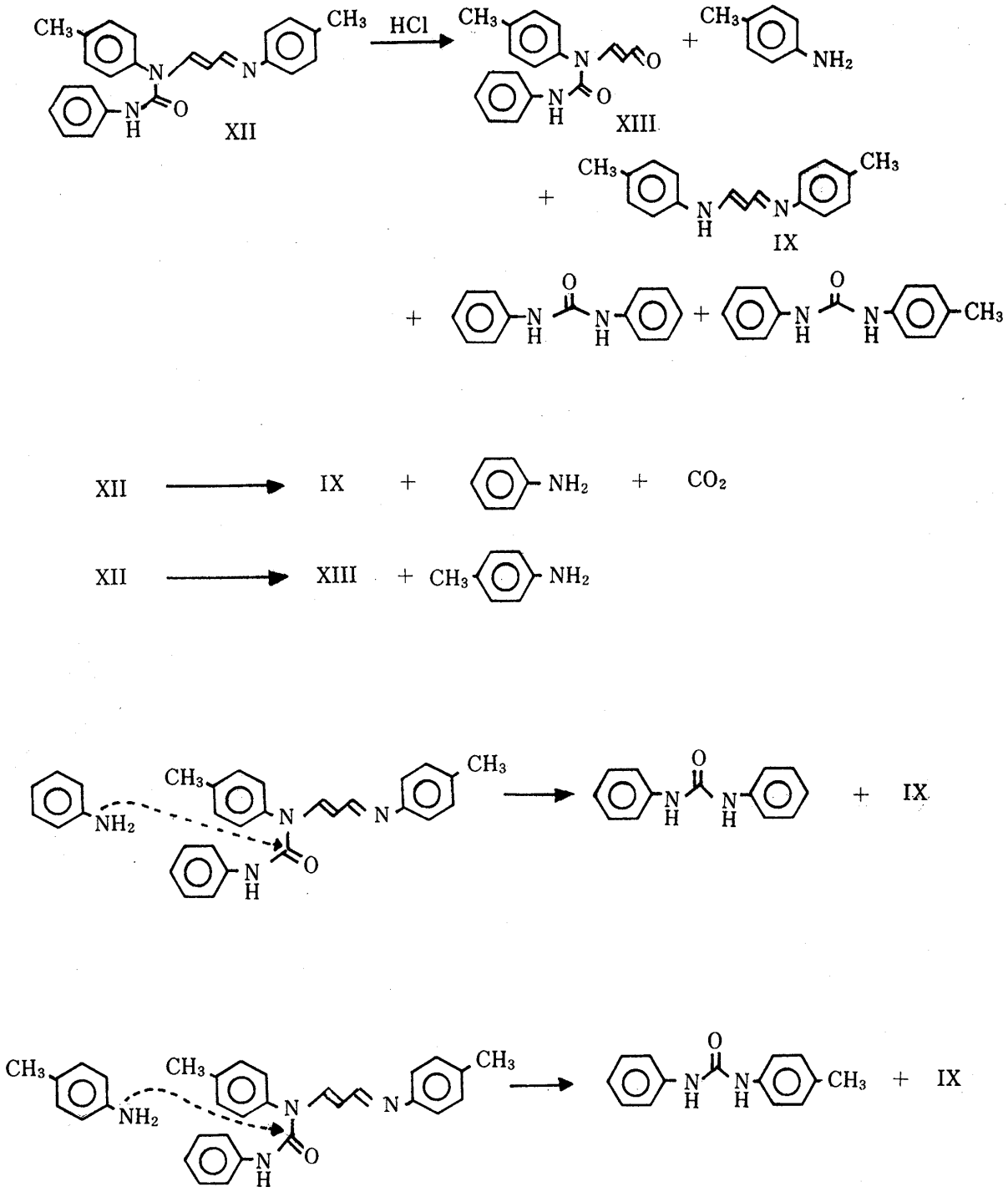
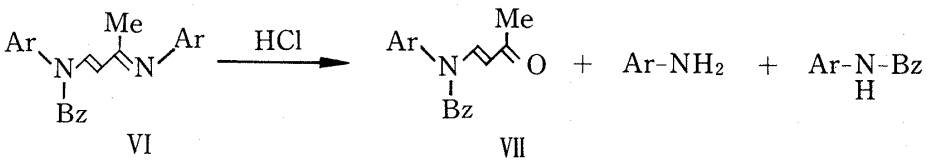
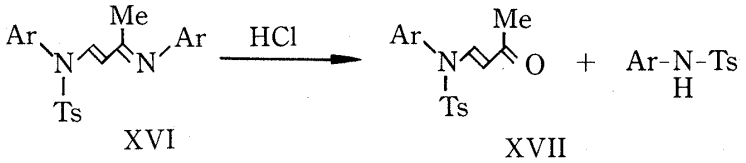


Chart 3

was allowed to stand for 2 days at room temperature. The reaction sequences was followed by ^{1}H-NMR spectroscopy of the reaction solution in deuterium oxide–dioxane-d_8 containing acetic acid-d_4 and potassium deuteroacetate. The spectrum of X in dioxane-d_8 showed signals at δ 1.87 (methyl, singlet), 5.22 (2-position, double doublet, J=9, 14 Hz), 8.18 (1-position, doublet, J=9 Hz) and 8.25 (3-position, doublet, J=14 Hz). At 10 min after the addition of a deuterium oxide solution of acetic acid-d_4 and potassium deuteroacetate, weak signals of XI were observed at δ 4.93 (α-position, double doublet, J=8, 14 Hz) and 9.43 (aldehyde, doublet, J=8 Hz), besides the signals of X. After 78 min, weak signals of IX and I were



VI VII



XVI XVII

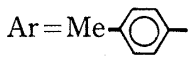


Chart 4

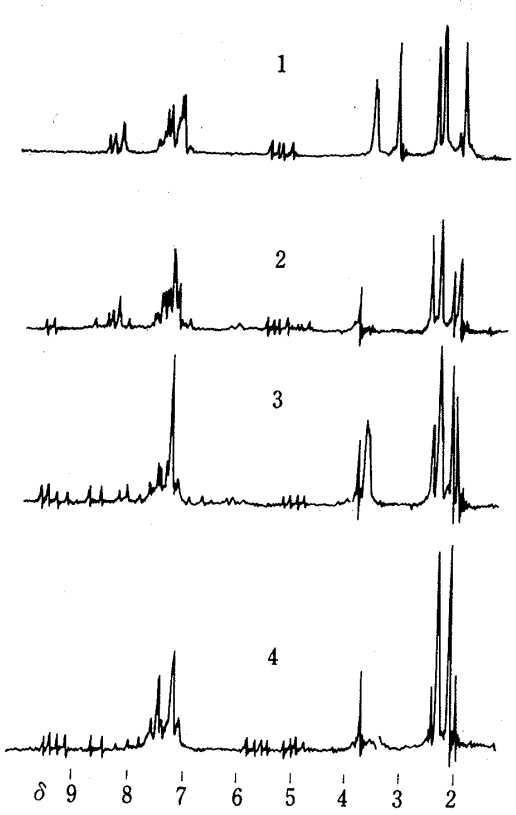


Fig. 1. Changes of the ^{1}H-NMR Spectrum of a D_2O–Dioxane-d_8 Solution of X in the Presence of CD_3COOD and CD_3COOK

1: the spectrum of X in dioxane-d_8.
2: at 10 min after the addition of D_2O solution of CD_3COOD and CD_3COOK.
3: at 78 min after the addition of D_2O solution of CD_3COOD and CD_3COOK.
4: at one day after the addition of D_2O solution of CD_3COOD and CD_3COOK.

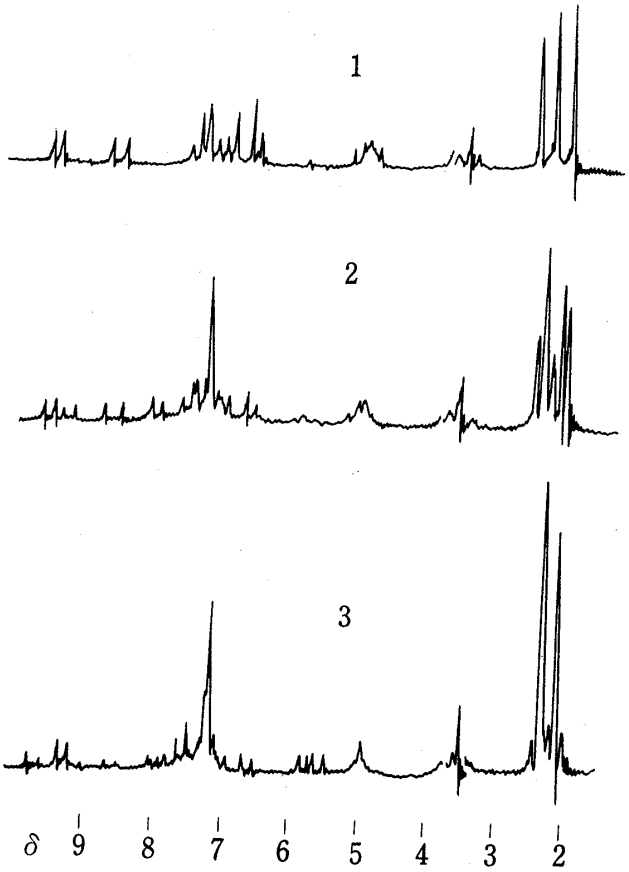


Fig. 2. Changes of the ^{1}H-NMR Spectrum of the Reaction Solution of Equimolar Amounts of XI and *p*-Toluidine in D_2O–Dioxane-d_8 in the Presence of CD_3COOD and CD_3COOK

1: immediately after dissolution.
2: at 175 min after dissolution.
3: at one day after dissolution.

observed at δ 6.00 (2-position of IX, triplet, J=10 Hz), 8.03 (1- and 3-position of IX, doublet, J=10 Hz), 5.63 (α-position of I, double doublet, J=9, 14 Hz) and 9.18 (aldehyde of I, doublet, J=9 Hz) besides the above signals. After one day, the deuteroacetic acid salt of IX precipitated from the solution. In the spectrum of the filtrate, the signals of X had disappeared, and the signals of I and XI showed nearly equal intensities. After a further one day, the pattern of the spectrum showed almost no change (Fig. 1). The ^{1}H-NMR spectrum of an equimolar mixture of XI and *p*-toluidine showed weak signals of IX and of I besides those of XI and *p*-toluidine at 175 min after dissolution under the same conditions. After one day, the signals of I had become more intense and those of IX had almost disappeared, and no precipitate was observed (Fig. 2). The reaction of XI and *p*-toluidine, the reverse reaction of the first step of hydrolysis of X, is relatively slow, and aminolysis at the 1-position of X is faster than aminolysis at the β-position of XI.

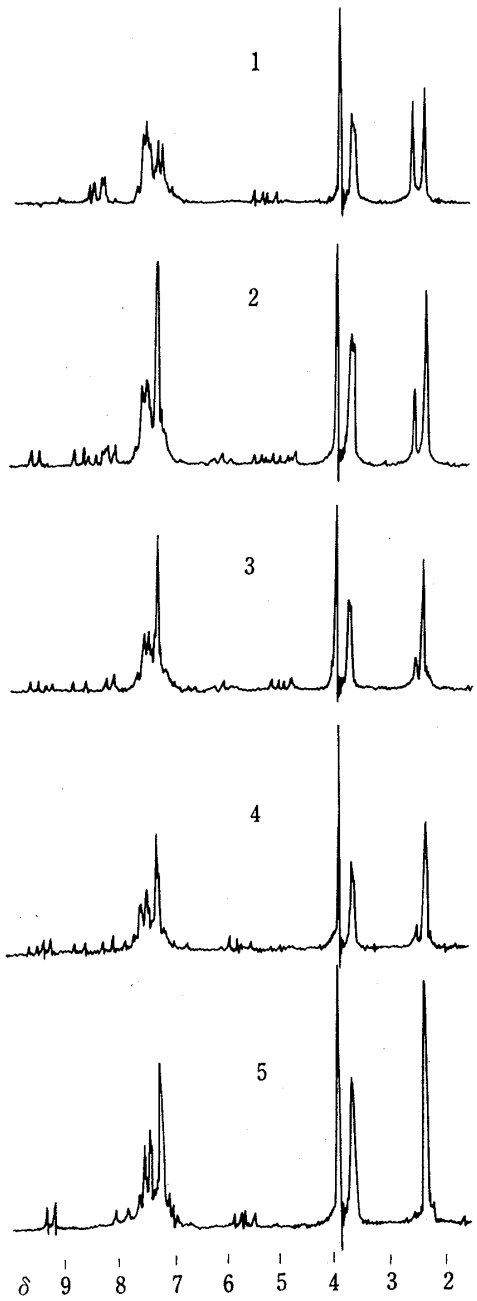


Fig. 3. Changes of the ^{1}H-NMR Spectrum of D_2O–Dioxane-d_8 Solution of XII in the Presence of CD_3COOD and CD_3COOK

1: immediately after dissolution.
2: at 70 min after dissolution.
3: at 295 min after dissolution.
4: at one day after dissolution.
5: at 7 days after dissolution.

N-Phenyl-*N'*-(*p*-methylphenyl)urea and I were obtained when a solution of XII in 80% aqueous dioxane containing equimolar amounts of acetic acid and sodium acetate was allowed to stand for 3 days at room temperature. Compound XIII could not be detected in the reaction solution. Evidence for the existence of XIII in the reaction solution was obtained from the ^{1}H-NMR spectrum of the reaction solution in deuterium oxide–dioxane-d_8 containing acetic acid-d_4 and potassium deuteroacetate. The spectrum showed signals of XII at δ 2.26 (methyl, singlet), 5.14 (2-position, double doublet, J=9, 14 Hz), 8.19 (3-position, doublet, J=9 Hz) and 8.27 (1-position, doublet, J=14 Hz) immediately after dissolution. After 70 min, signals of IX and XIII were observed at 5.94 (2-position of IX, triplet, J=10 Hz), 8.00 (β-position of XIII, doublet, J=14 Hz) and 9.40 (aldehyde of XIII, doublet, J=8 Hz) besides those of XII. After 295 min, the signals of IX and XIII were larger, weak signals of I were observed at δ 9.12 (aldehyde, doublet, J=9 Hz), and the signals of XII had disappeared. After 7 days, the spectrum showed a pattern identical with that of a mixture of I and *N*-phenyl-*N'*-(*p*-methylphenyl)urea (Fig. 3).

N-Tosyl-*p*-toluidine, XV, I and a small amount of *N*-formyl-*p*-toluidine were obtained when a solution of XIV in 79% aqueous dioxane containing equimolar amounts of acetic acid and sodium acetate was heated at 100°C for 3.5 h. The formation of I is not attributable to hydrolysis at the 1-position of XIV but to aminolysis

at the β-position of XV because hydrolysis of XVI afforded XVII and IV under the same condition. The course of the formation of *N*-formyl-*p*-toluidine is not yet clear.

The ^{1}H-NMR spectrum of VIII in methanol-d_4 showed signals at δ 2.32 (methyl, singlet), 5.25 (α-position, double doublet, J=8, 14 Hz), 8.62 (β-position, doublet, J=14 Hz) and 9.50 (aldehyde, doublet, J=8 Hz). On addition of a solution of sodium hydroxide in deuterium oxide, the spectrum changed, and after 4 min, signals were observed at δ 2.12 (singlet), 5.19 (triplet, J=11 Hz) and 8.41 (doublet, J=11 Hz). These signals are attributable to the methyl group, α-position and formyl group of the conjugate base of I, respectively. Besides the above signals, a multiplet signal of the 2- and 6-positions of the benzoate ion was observed at δ 8.07. After 8 min, H–D exchange at the α-position of the conjugate base of I proceeded to about onehalf completion. Aqueous sodium hydrogen carbonate solution was added to the above solution, and the whole was extracted with ether. Benzoic acid was obtained from the aqueous layer. The ether layer was concentrated under reduced pressures and a mixture of ethanol and triethylamine was added to the residue, This solution was concentrated under reduced pressure. This operation was repeated to ensure the exchange of deuterium at the α-position of I by hydrogen. The residue was shown to be identical with I by comparison of the IR spectra. Compound I is relatively stable in alkaline solution, *i.e.*, about one-half of I was recovered from the solution when I was refluxed for 3.5 h in aqueous ethanol-tetrahydrofuran in the presence of sodium hydroxide, and no formation of IX could be observed in the solution. *N*,*N*′-Diphenylurea and IX were obtained when a solution of XII in 70% aqueous dioxane solution containing sodium hydroxide was allowed to stand for 3 days at room temperature. This means that alkaline hydrolysis of XII occurred at its carbamoyl group. *N*-Tosyl-*p*-toluidine, I and IX were obtained when a solution of XIV in 70% aqueous ethanol containing sodium hydroxide was refluxed for 3.5 h. Presumably the formation of I does not arise from hydrolysis at the 1-position of XIV, because II could not be obtained from a reaction solution in which XVI had been treated under the same conditions; *N*-tosyl-*p*-toluidine, *p*-toluidine and a small amount of *N*-formyl-*p*-toluidine were obtained. From the above observations it was concluded that alkaline hydrolysis of XIV occurred at the 3-position to form XV and *p*-toluidine, while aminolysis at the β-position of XV and 1-position of XIV affords I and IX, respectively. The remaining XV is hydrolyzed to form *N*-tosyl-*p*-toluidine under alkaline conditions. Actually, *N*-tosyl-*p*-toluidine was obtained when a solution of XV in aqueous dioxane-methanol containing sodium hydroxide was allowed to stand for 126 min at room temperature. The hydrolysis of the imino group of IX under alkaline conditions was also observed in aqueous ethanol–tetrahydrofuran solution in the presence of sodium hydroxide. On heating of the solution at 60°C for 3.5 h, I was obtained in 23% yield while 19% of IX was recovered. On refluxing of the solution for 3.5 h, I was obtained in 26% yield while 3% of IX was recovered.

It is well known that imines readily undergo acid-catalyzed hydrolysis while they resist alkaline hydrolysis.[6] *N*,*N*′-Diarylfomamidine undergoes alkaline hydrolysis to form initially arylamine and *N*-formylarylamine, and the latter compound undergoes successive hydrolysis to form arylamine and formic acid.[7] It is not surprising that IX underwent alkaline hydrolysis because IX can be regarded as a vinylog of amidine'

The preparation of 3-(*N*-acylarylamino)-1-arylimino-2-butene will be reported later.

Experimental

All melting points are uncorrected. The ^{1}H-NMR spectra were recorded on a JNM-PMX 60 NMR spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used: singlet (s), doublet (d) and double doublet (dd).

Compounds XII and XIII were prepared according to the previous paper.[1] Compounds III, IV, V, VI, VII and VIII were prepared according to an earlier paper[4] and compounds I, IX, X and XI were also prepared by previously reported method.[8]

The samples of I, VII, VIII, IX, XI, XIII, *N*-benzoyl-*p*-toluidine, *N*-tosyl-*p*-toluidine, *p*-toluidine, *N*,*N*′-diphenylurea and *N*-phenyl-*N*′-(*p*-methylphenyl)urea described in this section were identical with the corresponding authentic sample on the basis of mixed melting point measurement and comparison of IR spectra.

1-(*N*-Tosyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (XIV)——*p*-Toluenesulfonyl chloride (4.20 g) was added portionwise to a stirred solution of 5.00 g of IX and 2.44 g of triethylamine in 200 ml of CH_2Cl_2. The mixture was stirred for 2 h at room temperature, and washed with 7% $NaHCO_3$. The CH_2Cl_2 layer was dried over K_2CO_3 and concentrated under reduced presure. The residue was recrystallized from benzene to give 4.14 g (51%) of XIV. mp 176°C. *Anal.* Calcd for $C_{24}H_{24}N_2O_2S$: C, 71.26; H, 5.98; N, 6.93. Found: C, 71.34; H, 6.02; N, 6.83. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, CH_3, s), 2.33 (3H, CH_3, s), 2.42 (3H, CH_3, s) 5.33 (1H, 2-position, dd, J=10, 14 Hz), 7.81 (1H, 1-position, d, J=14 Hz) and 8.06 (1H, 3-position, J=10 Hz).

1-(*N*-Tosyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-butene (XVI)——*p*-Toluenesulfonyl chloride (3.56 g) was added portionwise to a stirred solution of 4.55 g of 1-(*p*-methylphenylamino)-3-(*p*-methylphenyl imino)-1-butene hydrochloride ($C_{18}H_{20}N_2 \cdot H_2O \cdot 1/2C_6H_6$)[4] and 6.8 g of triethylamine in 60 ml of CH_2Cl_2. The mixture was stirred for 1 h at room temperature, and washed with 7% $NaHCO_3$. The CH_2Cl_2 layer was dried over K_2CO_3 and concentrated under reduced pressure. The residue (6.26 g) was dissolved in a small amount of CH_2Cl_2 and petroleum ether was added to the solution. The precipitate was collected to give 4.81 g (68% of pure XVI. mp 126°C. *Anal.* Calcd for $C_{25}H_{26}N_2O_3S$: C, 71.74; H, 6.26; N, 6.69. Found: C, 71.26; H, 6.21; N, 6.32. ^{1}H-NMR ($CDCl_3$) δ: 1.97 (3H, CH_3, s), 2.30 (3H, CH_3, s), 2.35 (3H, CH_3, s), 2.45 (3H, CH_3, s), 5.27 (1H, 2-position, d, J=15 Hz) and 7.93 (1-position, d, J=15 Hz). Besides these signals, weak signals of the conformational isomer were observed at δ 4.92 (2-position, d, J=15 Hz) and 7.82 (1-posi tion, d, J=15 Hz).

HCl-Catalyzed Hydrolysis of V——A solution of 0.35 g of V in 4 ml of THF was added to 20 ml of 0.1 N HCl with stirring, and 20 ml of ether was added to the mixture. The whole was stirred for 16 min at room temperature. The precipitated HCl salt of IX was collected and treated as usual to give 10 mg of IX. The ether layer of the filtrate was washed with 3 ml of 0.1 N HCl and extracted with 7% $NaHCO_3$. The ether layer was evaporated to dryness and the residue was recrystallized from EtOH to give 90 mg of VIII, the mother liquor was evaporated to dryness and the residue was subjected to preparative thin-layer chromatography (silica gel) with benzene–AcOEt (4: 1) as a developing solvent to give a small amount of *N*-benzoyl-*p*-toluidine. The HCl layer was treated as usual to give 40 mg of *p*-toluidine. No organic substance could be detected in the $NaHCO_3$ layer.

HCl-Catalyzed Hydrolysis of X——A warm solution of 0.73 g of X in 7 ml of THF was added to 50 ml of 0.1 N HCl with stirring, then 40 ml of ether was added to the mixture. The whole was stirred for 15 min at room temperature. The precipitated HCl salt of IX was collected and treated as usual to give 30 mg of IX. The ether layer of the filtrate was washed successively with 10 ml of 0.1 N HCl and 7% $NaHCO_3$ and concentrated. The residue (0.45 g) was recrystallized from petroleum benzine to give 0.28 g of XI. The HCl layer was treated as usual to give 90 mg of *p*-toluidine. No organic substance could be detected in the $NaHCO_3$ layer.

HCl-Catalyzed Hydrolysis of XIV——A warm solution of 2.02 g of XIV in 20 ml of THF was added to 100 ml of 0.1 N HCl with stirring, and 50 ml of ether was added to the mixture. The whole was stirred for 135 min at room temperature. The precipitated HCl salt of IX was collected and treated as usual to give 60 mg of IX. The ether layer of the filtrate was washed successively with 10 ml of 0.1 N HCl, 7% $NaHCO_3$ and 1 N NaOH, and concentrated. The residue was recrystallized from petroleum benzine to give 1.24 g of XV. mp 125°C. *Anal.* Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 65.12; H, 5.50; N, 4.38. ^{1}H-NMR ($CDCl_3$) δ: 2.37 (3H, CH_3, s), 2.45 (3H, CH_3, s), 5.00 (1H, α-position, dd, J=8, 14 Hz), 8.17 (1H, β-position, d, J=14 Hz) and 9.47 (1H, aldehyde, J=8 Hz). The HCl layer was treated as usual to give 0.26 g of *p*-toluidine. The NaOH layer was treated as usual to give 0.11 g of *N*-tosyl-*p*-toluidine. No organic substance could be detected in the $NaHCO_3$ layer.

HCl-Catalyzed Hydrolysis of XII——A warm solution of 0.74 g of XII in 7 ml of THF was added to 40 ml of 0.1 N HCl with stirring, and 40 ml of ether was added to the mixture. The whole was stirred for 10 min at room temperature. The precipitated HCl salt of IX was collected and treated as usual to give 90 mg of IX. The ether layer of the filtrate was washed successively with 0.05 N HCl and 7% $NaHCO_3$ and concentrated. A small amount of $CHCl_3$ was added to the residue, and the precipitated *N*,*N*′-diphenylurea (50 mg) was collected. It was shown to be identical with an authentic sample of comparison of their IR spectra. However, the mass spectrum of the sample showed a small peak at *m*/*z* 226, suggesting that a small amount of *N*-phenyl-*N*′-(*p*-methylphenyl)urea was contained in the sample. The filtrate was concentrated, and recrystallization of the residue from EtOH gave 0.13 g of XIII. The HCl layer was made alkaline by the addition of $NaHCO_3$ and extracted with ether. On standing of the ether layer, *N*-phenyl-*N*′-(*p*-methylphenyl)urea (30 mg) precipitated and was collected. From the filtrate, 30 mg of *p*-toluidine was obtained by the usual treatment. No organic substance could be detected in the $NaHCO_3$ layer.

HCl-Catalyzed Hydrolysis of VI——A solution of 0.74 g of VI in 6 ml of THF was added to 40 ml of 0.1 N HCl with stirring, and 10 ml of ether was added to the mixture. The mixture was stirred for 60 min at room

temperature. The ether layer was washed successively with 0.05 N HCl and 7% $NaHCO_3$, and concentrated. Recrystallization of the residue from petroleum benzine gave 0.28 g of VII. The HCl layer was made alkaline by the addition of $NaHCO_3$ and extracted with ether. The ether layer was concentrated and precipitated *N*-benzoyl-*p*-toluidine (10 mg) was collected. From the filtrate, 95 mg of *p*-toluidine was obtained by the usual treatment. No organic substance could be detected in the $NaHCO_3$ layer.

HCl-Catalyzed Hydrolysis of XVI——A warm solution of 1.25 g of XVI in 8 ml of THF was added to 60 ml of 0.1 N HCl with stirring, and 40 ml of ether was added to the mixture. The whole was stirred for 65 min at room temperature. The ether layer was washed successively with 0.05 N HCl, 7% $NaHCO_3$ and 1 N NaOH. The ether layer was concentrated and the residue was recrystallized from petroleum benzine to give 0.87 g of XVII. mp 79.5°C. *Anal.* Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.89; H, 5.81; N, 4.45. ^{1}H-NMR ($CDCl_3$) δ: 2.17 (3H, CH_3, s), 2.38 (3H, CH_3, s), 2.47 (3H, CH_3, s), 5.02 (1H, 3-position, d, $J=14$ Hz) and 8.35 (1H, 4-position, d, $J=14$ Hz). The NaOH layer was treated as usual to give 30 mg of *N*-tosyl-*p*-toludine. No organic substance could be detected in the $NaHCO_3$ layer.

Buffer-Catalyzed Hydrolysis of XII——A solution of 0.40 g of AcOH and 0.90 g of $AcONa\cdot 3H_2O$ in 15 ml of H_2O was added to a solution of 2.46 g of XII in 60 ml of dioxane. The mixture was allowed to stand for 3 d at room temperature, and 15 ml of 7% $NaHCO_3$ was added. The whole was concentrated under reduced pressure, and extracted with benzene. The benzene layer was concentrated, and a small amount of ether was added to the residue. The insoluble part was collected and recrystallized from benzene to give 0.63 g of I. The filtrate was concentrated, and the residue was fractionated by high performance liquid chromatography on silica gel with a mixture of benzene and AcOEt to give 0.13 g of *N*-phenyl-*N'*-(*p*-methylphenyl)urea and a small amount of *N*-formyl-*p*-toluidine.

Buffer-Catalyzed Hydrolysis of XIV——A solution of 0.60 g of AcOH and 1.36 g of $AcONa\cdot 3H_2O$ in 100 ml of H_2O was added to a solution of 4.04 g of XIV in 235 ml of dioxane. The mixture was heated at 100°C for 3.5 h, and 120 ml of 7% $NaHCO_3$ was added. The whole was distilled under reduced pressure on a water bath, and the residue was extracted with benzene. The distillate was made acidic by addition of HCl and concentrated under reduced pressure. The residue was treated as usual to give 10 mg of *p*-toluidine. The benzene solution was extracted with 1 N NaOH. The NaOH layer was treated as usual to give 1.43 g of *N*-tosyl-*p*-toluidine. The benzene layer was concentrated, and the residue was fractionated by high performance liquid chromatography on silica gel with a mixture of benzene and AcOEt to give 0.36 g of I, 0.10 g of XV and 10 mg of *N*-formyl-*p*-toluidine.

Buffer-Catalyzed Hydrolysis of XVI——A solution of 0.30 g of AcOH and 0.68 g of $AcONa\cdot 3H_2O$ in 17 ml of H_2O was added to a solution of 2.09 g of XVI in 40 ml of EtOH. The mixture was heated at 60°C for 24 h, and 30 ml of $NaHCO_3$ was added. The whole was distilled under reduced pressure on a water bath, and the residue was extracted with benzene. The distillate was made acidic by addition of HCl and concentrated under reduced pressure, then the residue was treated as usual to give a small amount of *p*-toluidine. The benzene extract was evaporated to dryness, and the residue was fractionated by high performance liquid chromatography on silica gel with a mixture of benzene and AcOEt to give 0.42 g of *N*-tosyl-*p*-toludine, 20 mg of IV and a small amount of XVII.

Alkaline Hydrolysis of XII——Compound XII (1.84 g) was dissolved in 35 ml of dioxane, and 5 ml of 1 N NaOH and 15 ml of H_2O were added to the solution. The mixture was allowed to stand for 3 d at room temperature. The resultant precipitate was collected and recrystallized from benzene to give 0.48 g of *N*,*N'*-diphenylurea. The mass spectrum of the sample showed a small peak at *m/z* 226, suggesting that a small amount of *N*-phenyl-*N'*-(*p*-methylphenyl)urea was contained in the sample. Ten ml of 7% $NaHCO_3$ was added to the filtrate, and the mixture was concentrated under reduced pressure. The residue was extracted with benzene, and the extract was concentrated. The residue was recrystallized from benzene to give 0.35 g of IX.

Alkaline Hydrolysis of XIV——Compound XIV (1.50 g) was dissolved in 50 ml of 70% EtOH containing 0.08 g of NaOH. The solution was refluxed for 3.5 h, and 7% $NaHCO_3$ was added. The mixture was distilled under reduced pressure on a water bath and the residue was extracted with ether. The distillate was made acidic by addition of HCl and concentrated. The residue was treated as usual to give a small amount of *p*-toluidine. The ether solution was extracted with 1 N NaOH. The NaOH layer was treated as usual to give 0.13 g of *N*-tosyl-*p*-toluidine. The ether layer was concentrated and the residue was fractionated by high performance liquid chromatography on silica gel with a mixture of benzene and AcOEt to give 0.41 g of *N*-tosyl-*p*-toluidine, 23 mg of I and 24 mg of IX.

Alkaline Hydrolysis of XVI——Compound XVI (1.00 g) was dissolved in 80 ml of 70% EtOH containing 98 mg of NaOH. The solution was refluxed for 4 h, and 15 ml of 7% $NaHCO_3$ was added. The mixture was concentrated under reduced pressure, and the residue was extracted with ether. The ether solution was extracted with 1 N NaOH. The NaOH layer was treated as usual to give 0.37 g of *N*-tosyl-*p*-toluidine. The ether layer was concentrated, and the residue was applied to a silica gel column and eluted with benzene–AcOEt to give a small amount of *p*-toluidine and 5 mg of *N*-formyl-*p*-toludine.

Alkaline Hydrolysis of XV——Compound XV (0.16 g) was dissolved in 1 ml of THF with warming at 60°C, and 0.6 ml of 1 N NaOH, 0.5 ml of H_2O and 2 ml of MeOH were added to the solution. The mixture was allowed to stand for 126 min at room temperature, then 10 ml of 7% $NaHCO_3$ was added. The whole

was concentrated under reduced pressure, and the residue was extracted with ether. The ether solution was extracted with 1 N NaOH. The NaOH layer was treated as usual to give 90 mg of *N*-tosyl-*p*-toludine.

Alkaline Hydrolysis of IX——Ten ml of 1 N NaOH and 20 ml of EtOH were added to a solution of 1.25 g of IX in 20 ml of THF. The mixture was heated at 60°C for 3.5 h, and 20 ml of 7% $NaHCO_3$ was added. The whole was concentrated under reduced pressure, and the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was concentrated, and a small amount of EtOH was added to the residue. The insoluble part was collected to give 0.18 g of unreacted IX. The filtrate was concentrated, and a solution of NaOEt in EtOH (made from 0.2 g of Na and 10 ml of EtOH) was added to the residue. The mixture was concentrated under reduced pressure, and the residue was extracted with ether. The ether solution was treated as usual to give 60 mg of IX. The residue was treated with 7% $NaHCO_3$, and the precipitate was collected and recrystallized from benzene to give 0.18 g of I.

References and Notes

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