[Chem. Pharm. Bull. 29(2) 308—317 (1981)]

Hydrolysis of Acyl Derivatives of Malonaldehyde Dianil. I

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(Received June 23, 1980)

The hydrolysis of acyl derivatives of malonaldehyde dianil was examined. Alkaline hydrolysis of 1-(*N*-acetyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (V) in aqueous ethanol gave simply 1-(*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (malonaldehyde dianil of *p*-toluidine) (VI) and acetic acid. Hydrolysis of 1-(*N*-benzoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (VII) in aqueous dioxane in the presence of equimolar amounts of acetic acid and sodium acetate gave β-(*p*-toluidino)acrolein (VIII), β-(*N*-benzoyl-*p*-toluidino)acrolein (XIII) and *N*-benzoyl-*p*-toluidine. A small amount of β-(*p*-toluidino)crotonaldehyde (II) was obtained by hydrolysis of 1-(*N*-benzoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-butene (IX).

The buffer-catalyzed hydrolysis reaction of VII was followed by measuring the PMR spectrum of the reaction solution to elucidate the sequence of the reaction process.

Keywords——hydrolysis; 1-(*N*-benzoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene; 1-(*N*-benzoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-butene; 1-(*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-butene; 1,3-bis(*N*-benzoyl-*p*-toluidino)-1,3-butadiene; β-(*p*-toluidino)acrolein; β-(*N*-benzoyl-*p*-toluidino)acrolein; 4-(*p*-toluidino)-3-buten-2-one; 4-(*N*-benzoyl-*p*-toluidino)-3-buten-2-one

In the previous paper[1] we reported a preparative method for β-arylaminoacrolein derivatives by reversible hydrolysis of malonaldehyde dianil in the presence of acetic acid and sodium acetate (equation 1, Chart 1). This method has the advantage over the customary method,[2] which is based on the reaction of β-ethoxyacrolein and primary arylamines, that β-arylaminoacroleins derived from weakly basic arylamines, such as *o*-chloroaniline, can be prepared.

Preparation of β-arylaminocrotonaldehyde, a possible reactant in the Combes reaction, by hydrolysis of 1-arylamino-3-arylimino-1-butene was attempted, since efforts to prepare β-arylaminocrotonaldehyde from arylamine and tetrolaldehyde or β-methoxycrotonaldehyde had been unsuccessful. 1-(*p*-Methylphenylamino)-3-(*p*-methylphenylimino)-1-butene hydrochloride (I) was prepared from β-chlorocrotonaldehyde and *p*-toluidine according to the procedure used for preparation of 1-phenylamino-3-phenylimino-1-butene hydrochloride by Gagan and Lloyd.[3]

Hydrolysis of I in the presence of acetic acid and sodium acetate, however, did not give β-(*p*-toluidino)crotonaldehyde (II) but yielded 4-(*p*-toluidino)-3-buten-2-one (III) (equation 2, Chart 1). The latter was identified by comparison with an authentic sample prepared according to Thielepape.[4]

Examination of the hydrolysis of *N*-acyl derivatives of malonaldehyde dianil was attempted. Assuming that bond scission occurs between the 1-position and the nitrogen atom of 1-(*N*-acylarylamino)-3-arylimino-1-propene (IV) in the hydrolysis process to form *N*-acylarylamine and β-arylaminoacrolein (equation 3, Chart 1), hydrolysis of 1-(*N*-acylarylamino)-3-arylimino-1-butene would be expected to give β-arylaminocrotonaldehyde (for example equation 4, Chart 1). Further, for the preparation of β-arylaminoacrolein derivatives, hydrolysis of IV would be advantageous as compared with that of malonaldehyde dianil itself, because the hydrolysis of IV may be irreversible.

Previously[5] we reported the preparation of 1-(*N*-acetyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (V) by the reaction of 1-(*p*-methylphenylamino)-3-(*p*-methyl-

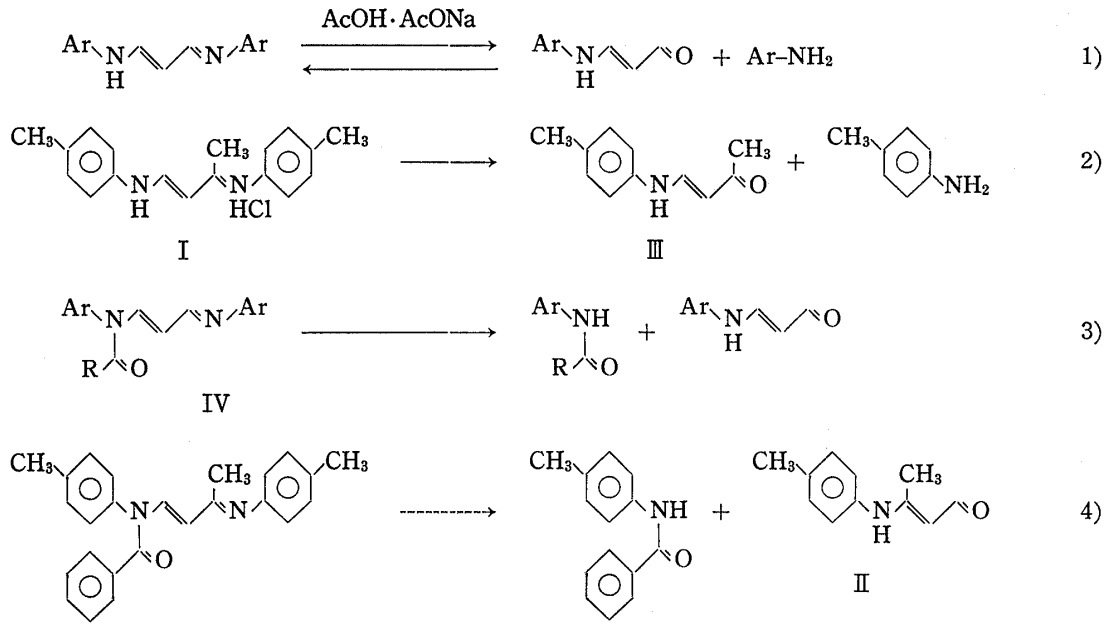

Chart 1

phenylimino)-1-propene (malonaldehyde dianil of *p*-toluidine) (VI) and acetyl chloride in the presence of triethylamine. In a similar manner, 1-(*N*-benzoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (VII) was prepared from VI and benzoyl chloride. VI, benzoic acid, *p*-toluidine and *β*-(*p*-toluidino)acrolein (VIII) were formed on heating 70% aqueous ethanolic solution of VII at 60° for 9 hr in the presence of an equimolar amount of sodium hydroxide. Presumably VII was hydrolyzed to form benzoic acid and VI at the first step, and a part of the latter was further hydrolyzed to form *p*-toluidine and VIII during the reaction period. Hydrolysis of V proceeded much more readily than that of VII, so that the formation of acetic acid and VI was virtually completed in 70% aqueous ethanol within 40 min at room temperature in the presence of an equimolar amount of sodium hydroxide, and neither *p*-toluidine nor VIII was detected in the reaction mixture. Davis[6] reported that the second-order rate constant of hydrolysis of *N*-benzoyl-*p*-nitroaniline in aqueous sodium hydroxide solution at boiling point is 3.65×10^{-3} sec^{-1} mol^{-1}, and that the rate of hydrolysis of *N*-acetyl-*p*-nitroaniline is too fast to estimate the rate constant under the same conditions. Meresaar and Bratt[7] reported that the rate of hydrolysis of acetamide in aqueous sodium hydroxide solution at 45° is five times as fast as that of benzamide. The rate of alkaline hydrolysis of VII is much slower than that of V, and 36% of VII was recovered from the reaction solution in which VII had been heated for 1 hr at 60° in 70% aqueous ethanol in the presence of an equimolar amount of sodium hydroxide.

When I and benzoyl chloride were reacted in dichloromethane in the presence of triethylamine, 1-(*N*-benzoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-butene (IX) was obtained as pale yellow crystals melting at 140°. The results of elemental analysis of IX were consistent with the values required for the molecular formula $C_{25}H_{24}N_2O$, and another possible structure, 3-(*N*-benzoyl-*p*-methylphenylamino)-1-(*p*-methylphenylimino)-2-butene (X), was ruled out by the proton magnetic resonance (PMR) spectrum, *i. e.*, signals of the 1- and 2-position were observed at δ 8.27 ppm (doublet, $J=15$ Hz) and 5.60 ppm (doublet, $J=15$ Hz), respectively, in deuterochloroform.[8] The relatively large value of spin-spin coupling constant ($J=15$ Hz) suggests a *trans* double bond structure at the 1- and 2-position (Chart 3).

As a by-product in the preparation of IX, colorless crystals melting at 155° (XI) were obtained. The results of elemental analysis were consistent with the values required for the molecular formula $C_{32}H_{28}N_2O_2$. The structure of XI was determined to be 1,3-bis(*N*-benzoyl-

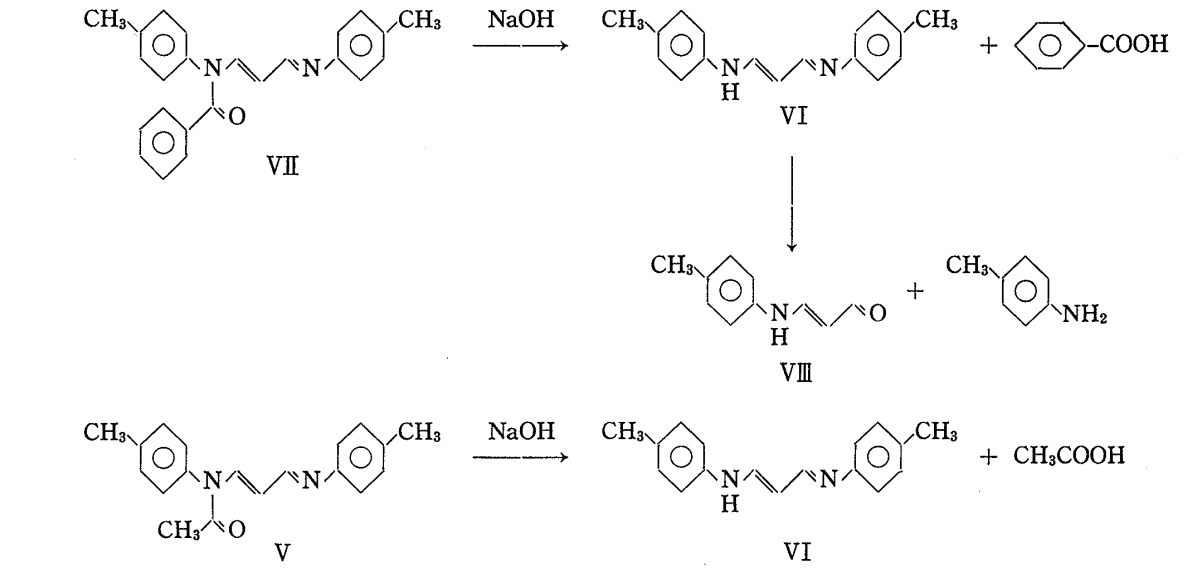

Chart 2

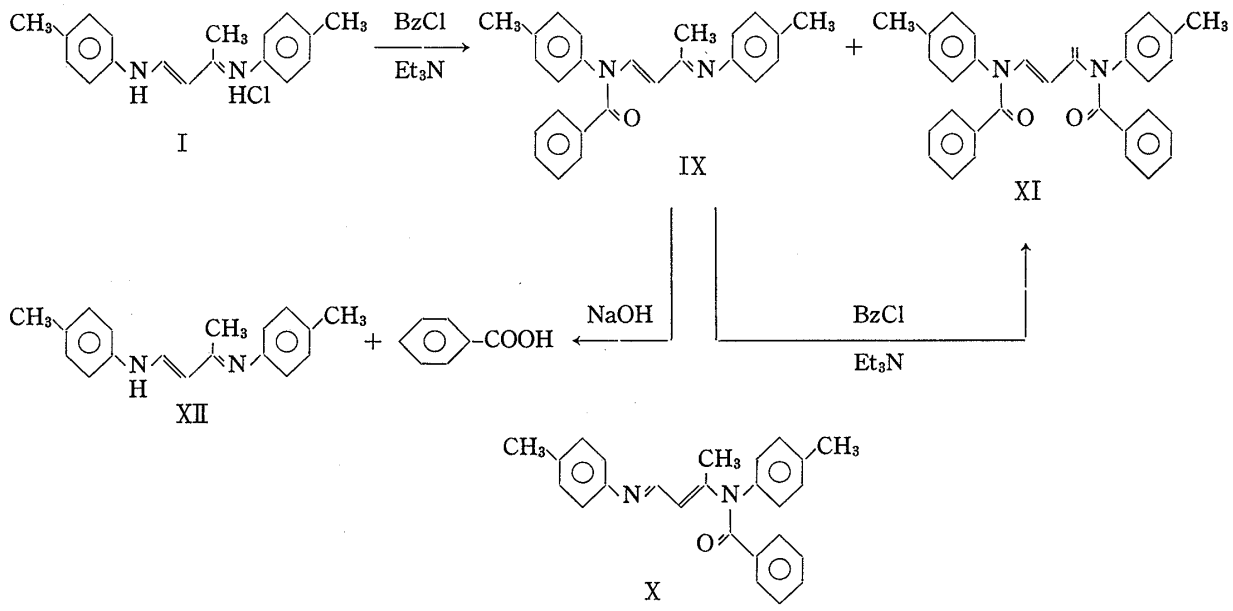

Chart 3

p-toluidino)-1,3-butadiene by spectroscopic analysis: *i. e.*, in the PMR spectrum of XI (deuterochloroform) signals of the 4-position were observed at δ 4.83 ppm (1H, singlet) and 5.02 ppm (1H, singlet). These two signals are not one doublet of 2H intensity; this was confirmed by comparison of the spectra recorded on 60 MHz and 100 MHz PMR spectrometers. The ^{13}C nuclear magnetic resonance spectrum (CMR spectrum) of XI showed signals of the 2- and 4-position at δ 111.62 ppm and 115.16 ppm, respectively, in deuterochloroform; the former split into a doublet and the latter split into a triplet under off-resonance conditions. XI was obtained in good yield by the reaction of IX and benzoyl chloride in the presence of triethylamine (Chart 3).

When IX was hydrolyzed in 70% aqueous ethanol in the presence of an equimolar amount of sodium hydroxide at room temperature, 1-(*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-butene (XII), which was difficult to obtain in a pure crystalline state by neutralization of I, was gradually precipitated from the solution, and after filtration, benzoic acid was obtained from the filtrate.

On heating at 60° for 4 hr in 80% aqueous dioxane solution in the presence of equimolar amounts of acetic acid and sodium acetate, VII was hydrolyzed to form VIII, β-(*N*-benzoyl-*p*-toluidino)acrolein (XIII) and *N*-benzoyl-*p*-toluidine. XIII was identified by comparison with an authentic sample prepared from VIII and benzoic anhydride in the manner described for β-(*N*-acetyl-*p*-toludino)acrolein (XIV).[5] The structure of XIII was confirmed by its PMR spectrum (dioxane-d_8), *i.e.*, signals of XIII were observed at δ 5.22 ppm (1H, double doublet, J=8 and 14 Hz, α-position), 8.52 ppm (1H, doublet, J=14 Hz, β-position) and 9.52 ppm (1H, doublet, J=8 Hz, aldehyde), suggesting that the 2-propenal structure is retained in XIII, namely that the benzoyl group combines not with oxygen but with nitrogen . V was hydrolyzed on standing at room temperature for 2 days in 80% aqueous dioxane solution in the presence

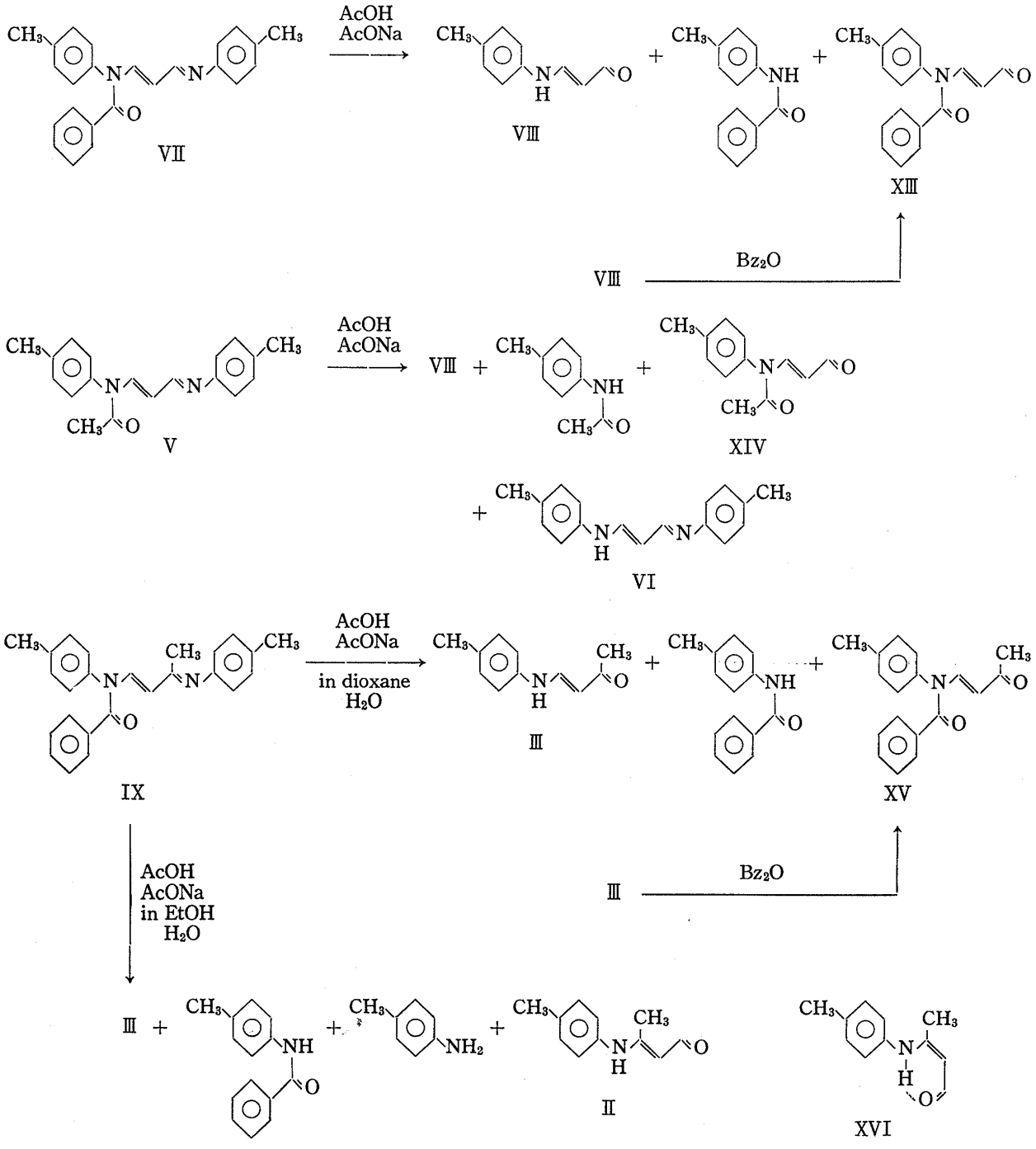

Chart 4

of equimolar amounts of acetic acid and sodium acetate. VIII, XIV, *N*-acetyl-*p*-toluidine and VI were obtained from the reaction mixture (Chart 4).

III, 4-(*N*-benzoyl-*p*-toluidino)-3-buten-2-one (XV), *N*-benzoyl-*p*-toluidine and a trace of *N*-formyl-*p*-toluidine were obtained when IX was heated at 60° for 2 hr in 80% aqueous dioxane solution in the presence of equimolar anmouts of acetic acid and sodium acetate. XV was identified by copmarison with an authentic sample prepared from III and benzoic anhydride. Hydrolysis of IX in 80% aqueous ethanol under the same conditions, as employed in the hydrolysis experiment in 80% aqueous dioxane, afforded III, *N*-benzoyl-*p*-toluidine, *p*-toluidine and a small amount of II as white needles melting at 91°. The results elemental analysis of II were consistent with the values required for the molecular formula $C_{11}H_{13}NO$. The PMR spectrum of II in deuterochloroform showed signals at δ 5.12 ppm (1H, doublet, $J=$ 3 Hz, α-position) and 9.05 ppm (1H, doublet, $J=3$ Hz, aldehyde). The small value of spin-spin coupling constant ($J=3$ Hz) suggests that II exists in the s-*cis* form (XVI, Chart 4) in this solvent.

The course of the hydrolysis reaction of VII was followed by PMR spectroscopy of the reaction solution at 37° to elucidate the sequence of the reaction. The PMR spectrum of VII in dioxane-d_8 showed signals at δ 5.52 ppm (1H, double doublet, $J=9$ and 14 Hz, 2-position), 8.25 ppm (1H, doublet, $J=9$ Hz, 3-position) and 8.35 ppm (1H, doublet, $J=14$ Hz, 1-position). At 1.5 hr after addition of a deuterium oxide solution of acetic acid-d_4 and potassium carbonate to the dioxane-d_8 solution of VII, new signals were observed, besides those of VII, at δ 5.23 ppm (double doublet, $J=8$ and 14 Hz) 8.57 ppm (doublet, $J=14$ Hz) and 9.55 ppm (doublet, $J=8$ Hz) in the PMR spectrum. These signals showed

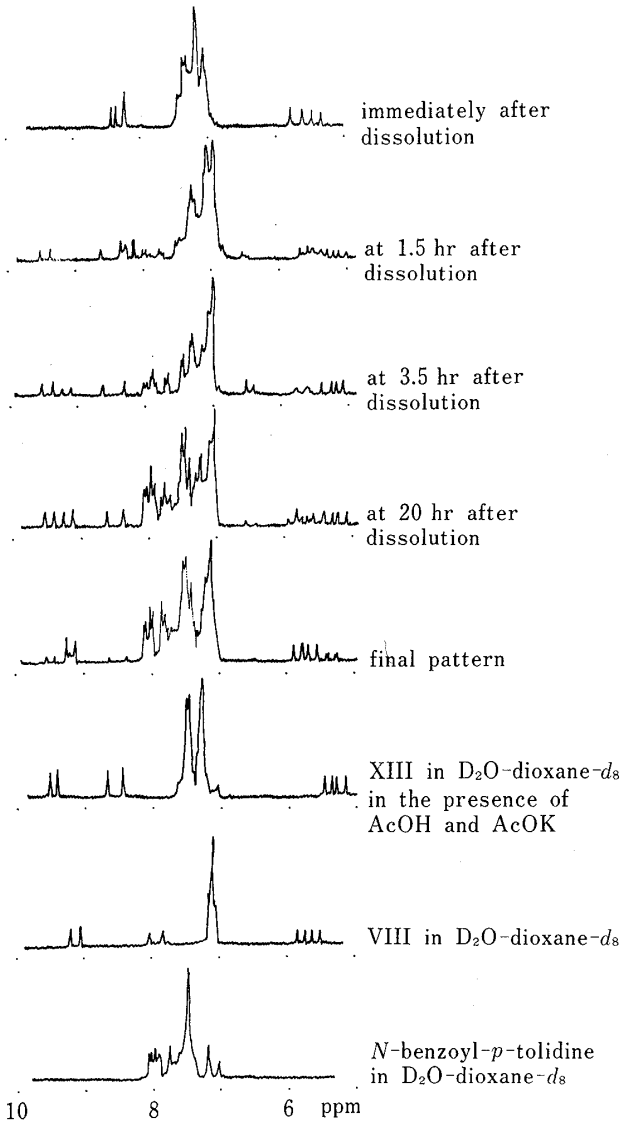

Fig. 1. Change of the PMR Spectrum of VII in D_2O–Dioxane-d_8 in the Presence of CD_3COOD and CD_3COOK at 37°

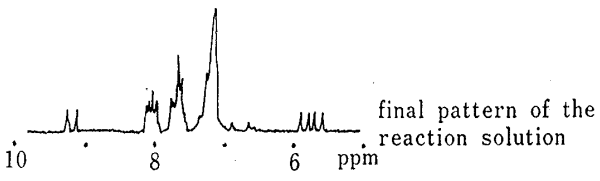

Fig. 2. PMR Spectrum of the Reaction Solution of XIII and *p*-Toluidine in D_2O–Dioxane-d_8 in the Presence of CD_3COOD and CD_3COOK at room temperature

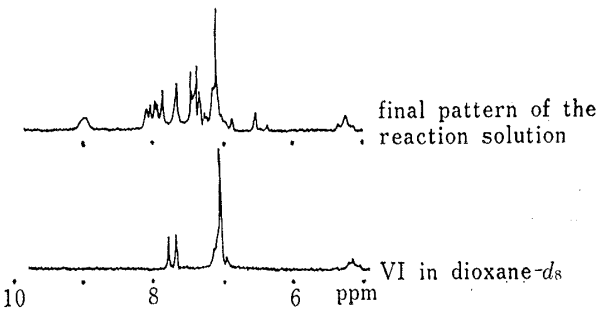

Fig. 3. PMR Spectrum of the Reaction Solution of VII and *p*-Toluidine in Dioxane-d_8 at room temperature

a pattern identical with that of XIII. After 3.5 hr, a small doublet signal (J=9 Hz) was observed at δ 9.25 ppm, and a triplet signal (J=9 Hz) was observed at δ 5.80 ppm. The former is assigned as the signal of the aldehydic proton of VIII and the latter as that of the 2-position of VI. The signals of VII became smaller than those of XIII. At the same time, a small amount of a yellow crystalline mass was precipitated from the solution. A similar crystalline mass, mp 122°, was obtained from the hydrolysis of VII with aqueous dioxane containing acetic acid and sodium acetate, and it was identified as the acetic acid salt of VI. After 20 hr, the crystalline mass of acetic acid-d_4 salt of VI still remained in the reaction mixture. On heating the mixture at 60° for few minutes, the crystalline mass dissolved easily, but it reprecipitated on standing at 37°. In the PMR spectrum of the mixture, the signal of the α-position of VIII was observed at δ 5.67 ppm (double doublet, J=9 and 13 Hz), and signals of VIII showed intensities similar to those of XIII. No signal of VII could be detected. Finally, the crystalline mass of acetic acid-d_4 salt of VI disappeared, and the PMR spectrum of the solution showed a pattern identical with that of a mixture of VIII and *N*-benzoyl-*p*-toluidine (Fig. 1).

On the other hand, the PMR spectrum of XIII in dioxane-d_8 did not change on addition of a solution of acetic acid-d_4 and potassium carbonate in deuterium oxide. On addition of *p*-toluidine to the above solution, a yellow crystalline mass of the acetic acid-d_4 salt of VI gradually precipitated. When the precipitate had disappeared, signals of VIII (at δ 5.60 and 9.15 ppm) gradually increased in intensity and the final pattern of the PMR spectrum of the solution was identical with that of a 1:1 mixture of VIII and *N*-benzoyl-*p*-toluidine in the same medium (Fig. 2).

The reaction of VII and *p*-toluidine was also followed by PMR spectroscopy of the reaction solution at room temperature. At 2 days after dissolution of VII and *p*-toluidine in dioxane-d_8, the PMR spectrum of the solution showed signals at δ 5.23 ppm (triplet, J=8 Hz) and 7.03 ppm (diffused singlet), and the pattern of the signals in the range of δ 7.50—8.00 ppm closely resembled that of *N*-benzoyl-*p*-toluidine. The PMR spectrum of VI in dioxane-d_8 showed signals at δ 5.14 ppm (1H, triplet, J=8 Hz, 2-position), 7.08 ppm (8H, diffused singlet, aromatic ring) and 7.75 ppm (2H, doublet, J=8 Hz, 1- and 3-position). The PMR spectrum of the reaction solution ,therefore, showed a pattern identical with that of a 1:1 mixture of VI and *N*-benzoyl-*p*-toluidine (Fig. 3).

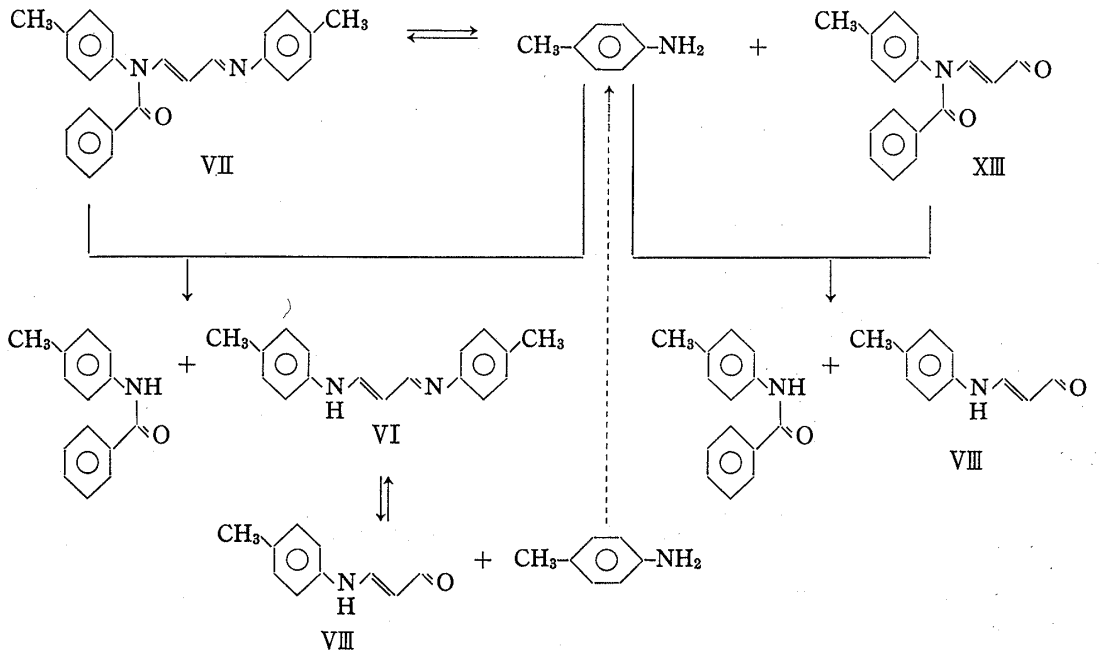

Chart 5

In view of these observations, the main route of hydrolysis of VII in the presence of acetic acid and sodium acetate was elucidated to be as shown in Chart 5: first, VII undergoes reversible hydrolysis to give XIII and *p*-toluidine. Further, XIII and *p*-toluidine react to give VIII and *N*-benzoyl-*p*-toluidine; this process may be irreversible. A part of the *p*-toluidine reacts with VII to give VI and *N*-benzoyl-*p*-toluidine, and VI undergoes reversible hydrolysis to give VIII and *p*-toluidine under these conditions. Buffer-catalyzed hydrolysis of VI was found to be reversible and markedly affected by the acidity of the medium.[1] Hydrolysis of VI does not proceed in the presence of equimolar amounts of acetic acid and sodium acetate, because the high acidity of the medium favors the reverse reaction.[1] In the present case, however, the reaction of XIII and *p*-toluidine, together with that of VII and *p*-toluidine, consumes *p*-toluidine by irreversible formation of VIII and *N*-benzoyl-*p*-toluidine. As the overall process, VII undergoes irreversible hydrolysis to form VIII and *N*-benzoyl-*p*-toluidine in the presence of acetic acid and sodium acetate.

In the hydrolysis reaction of IX, a small amount of II was obtained from reaction mixture. This suggests that a minor pathway, in which bond scission occurs between the 1-position and the nitrogen atom of VII to give VIII and *N*-benzoyl-*p*-toluidine directly, proceeds in parallel to the above-mentioned main course.

It appears that the preparation of II by hydrolysis of IX may be difficult in view of the above-mentioned sequence of the hydrolysis reaction of VII.

Experimental

All melting points are uncorrected. The PMR 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), double doublet (dd) and triplet (t).

1-(*N*-Benzoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (VII)——A solution of 3.90 g (0.028 mol) of BzCl in 50 ml of CH_2Cl_2 was added to a solution of 6.95 g (0.028 mol) of VI in 100 ml of CH_2Cl_2. The reaction solution was allowed to stand for 1 hr at room temperature, and then washed successively with 7% $NaHCO_3$ and H_2O. The solution was dried over K_2CO_3 and the solvent was removed under reduced pressure to give 8.70 g (88%) of crude VII. Recrystallization from benzene afforded 5.56 g (57%) of pure VII as pale yellow crystals. mp 168°. *Anal.* Calcd for $C_{24}H_{22}N_2O$: C, 81.33; H, 6.26; N, 7.90. Found: C, 81.25; H, 6.19; N, 7.75.

β-(*N*-Benzoyl-*p*-toluidino)acrolein (XIII)——A solution of 5.65 g (0.025 mol) of Bz_2O in 20 ml of benzene was added to a solution of 3.22 g (0.02 mol) of VIII and 4 g of Et_3N in 40 ml of benzene. The reaction solution was refluxed for 2.5 hr. The solution was washed successively with 7% $NaHCO_3$ and H_2O, and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was washed with a small amount of benzene, and recrystallized from EtOH to yield 1.39 g of XIII. The mother liquor was evaporated to dryness under reduced pressure, and the residue was fractionated by column chromatography on silica gel with benzene as an eluent. From the first fraction, 0.75 g of XIII was obtained by recrystallization from EtOH. Total yield of XIII, as white crystals melting at 116°, was 2.14 g (40%). *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.92; H 5.63; N, 5.37.

4-(*N*-Benzoyl-*p*-toluidino)-3-buten-2-one (XV)——4-(*p*-Toluidino)-3-buten-2-one (III) was prepared from *p*-toluidine and the Na salt of formylacetone according to the procedure used for the preparation of 4-anilino-3-buten-2-one by Thielepape.[5] mp 115.5°.[9]

A solution of 0.271 g (0.0012 mol) of Bz_2O in 4 ml of benzene was added to a solution of 0.175 g (0.001 mol) of III and 0.2 g (0.002 mol) of Et_3N in 6 ml of benzene. The reaction solution was refluxed for 22 hr, and washed successively with 7% $NaHCO_3$ and H_2O. The solution was dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel with a mixture of benzene and AcOEt as an eluent to give 0.055 g (20%) of XV as white crystals melting at 82°. *Anal.* Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.42; H, 6.04; N, 5.18. PMR ($CDCl_3$, δ): 2.25 ppm (3H, s, 1-position), 2.35 ppm (3H, s, aromatic CH_3), 5.35 ppm (1H, d, $J=15$ Hz, 3-position) and 8.63 ppm (1H, d, $J=15$ Hz, 4-position).

1-(*p*-Methylphenylamino)-3-(*p*-methylphenylimino)-1-butene Hydrochloride (I)——A solution of 25 g (0.24 mol) of β-chlorocrotonaldehyde in 70 ml of benzene was added to a solution of 51 g (0.48 mol) of *p*-toluidine in 300 ml of a mixture of benzene and EtOH (2: 1) under ice cooling. The reaction solution was allowed to stand for 3 days in a refrigerator. Orange crystals that precipitated were collected to yield 65 g (78%) of I. The crystals changed to a new shape at 111°, and decomposed at 192°. *Anal.* Calcd for $C_{18}H_{20}N_2 \cdot HCl \cdot 1/2H_2O \cdot 1/2C_6H_6$: C, 72.29; H, 7.22; N, 8.03. Found: C, 72.55; H, 7.50; N, 8.01. PMR (CD_3OD, δ): 2.30,

2.37 and 2.63 ppm (each 3H, s, $3\times CH_3$), 6.03 ppm (1H, d, $J=13$ Hz, 2-position) and 8.53 ppm (1H, d, $J=13$ Hz, 1-position). H-D exchange reaction was not observed. The signal of benzene contained in the crystals was observed at δ 7.37 ppm in the PMR spectrum. The crystals of I were dissolved in EtOH, and the solution was evaporated to dryness under reduced pressure. The PMR spectrum of the residue in CD_3OD showed no signal of benzene. However, the residue could not be crystallized.

1-(*N*-Benzoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-butene (IX)——A solution of 7.73 g (0.055 mol) of BzCl in 40 ml of CH_2Cl_2 was added to a solution of 17.45 g (0.05 mol) of I and 20.2 g (0.2 mol) of Et_3N in 200 ml of CH_2Cl_2, and the reaction solution was allowed to stand for 1 hr at room temperature. The solution was washed successively with 7% $NaHCO_3$ and H_2O, and dried over Na_2SO_4. The solvent was removed under reduced pressure to yield 17.6 g (96%) of crude IX. Recrystallization from a mixture of CH_2Cl_2 and petroleum ether afforded 14.58 g (79%) of pure IX. mp 140°. *Anal.* Calcd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60. Found: C, 81.52; H, 6.51; N, 7.43.

1,3-bis(*N*-Benzoyl-*p*-toluidino)-1,3-butadiene (XI)——A solution of 1.55 g (0.0011 mol) of BzCl in 10 ml of benzene was added to a solution of 3.68 g (0.01 mol) of IX and 2 g (0.02 mol) of Et_3N in 20 ml of benzene, and the reaction solution was allowed to stand overnight at room temperature. The solution was washed successively with 7% $NaHCO_3$ and H_2O, and dried over K_2CO_3. The solvent was removed under reduced pressure to yield 4.08 g (86%) of crude XI. Recrystallization from MeOH afforded 3.13 g (66%) of pure XI as white crystals melting at 155°. *Anal.* Calcd for $C_{32}H_{28}N_2O_2$: C, 81.33; H, 5.97; N, 5.93. Found: C, 81.56; H, 5.96; N, 5.82. PMR ($CDCl_3$, δ): 2.32 ppm (6H, s, $2\times CH_3$), 4.83 ppm (1H, s, 4-position), 5.02 ppm (1H, s, 4-position), 5.32 ppm (1H, d, $J=14$ Hz, 2-position) and 7.80 ppm (1H, d, $J=14$ Hz, 1-position).

1-(*p*-Methylphenylamino)-3-(*p*-methylphenylimino)-1-butene (XII)——Eighteen ml of H_2O and 20.5 ml of 1 N NaOH were added to a warm solution of IX in 80 ml of EtOH. The reaction mixture was stirred for 2 hr at room temperature. Pale yellow crystals were precipitated. The precipitate was filtered with suction to give 4.73 g (90%) of XII, mp 116°. The filtrate was allowed to stand at room temperature, and an additional 0.22 g of XII was precipitated. It was filtered off with suction. From the filtrate, 2.3 g (94%) of benzoic acid was obtained. *Anal.* Calcd for $C_{18}H_{20}N_2$: C, 81.76; H, 7.64; N, 10.60. Found: C, 81.90; H, 7.92; N, 10.75. PMR ($CDCl_3$, δ): 1.93 ppm (3H, s, 4-position), 2.27, 2.33 ppm (each 3H, s, $2\times CH_3$), 4.93 ppm (1H, d, $J=8$ Hz, 2-position) and 7.25 ppm (d, $J=8$ Hz, 1-position). The relative integrated intensity of the last signal could not be estimated owing to overlapping with the signals of aromatic hydrogen atoms. In CD_3OD solution signals of XII were observed at δ 2.13 ppm (3H, s, 4-position), 2.23, 2.28 ppm (each 3H, s, $2\times CH_3$), 5.47 ppm (1H, d, $J=12$ Hz, 2-position) and 7.60 ppm (1H, d, $J=12$ Hz, 1-position). The intensities of the signals of the 2- and 4-position became smaller on standing in CD_3OD owing to H-D exchange reaction, and after one day, the signals had completely disappeared, and the signal of the 1-position was observed as a singlet. The spin-spin coupling constants between the 1- and 2-position suggest that XII exists in the s-*cis* form in $CDCl_3$ and in the s-*trans* form in CD_3OD.

AcOH Salt of VI——A solution of 0.62 g (0.0025 mol) of VI and 0.15 g (0.0025 mol) of AcOH in 5 ml of $CHCl_3$ was allowed to stand for 2 hr under ice cooling. The precipitate was collected to yield 0.18 g (22%) of the AcOH salt of VI, mp 122°. *Anal.* Calcd for $C_{17}H_{18}N_2\cdot C_2H_4O_2\cdot H_2O$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.20; H, 7.30; N, 8.61. PMR (dioxane-d_8, δ): 1.97 ppm (3H, s, CH_3 of AcOH), 2.30 ppm (6H, s, aromatic CH_3), 5.33 ppm (1H, t, $J=8$ Hz, 2-position) and 7.77 ppm (2H, d, $J=8$ Hz, 1- and 3-position).

Hydrolysis of I in the Presence of AcOH and AcONa——A solution of 1.36 g (0.01 mol) of $AcONa\cdot 3H_2O$ in 12 ml of H_2O and 9 ml of 1 N NaOH were added to a solution of 3.49 g (0.01 mol) of I in 50 ml of EtOH. The reaction solution was heated at 60° for 18.5 hr on a water bath. After addition of 20 ml of 7% $NaHCO_3$, the solution was concentrated under reduced pressure to remove most of the EtOH. The distillate, after being made acidic by addition of HCl, was evaporated to dryness. From the residue, 0.243 g of *p*-toluidine was obtained. The concentrated reaction solution was extracted with ether, and the ether layer was dried over K_2CO_3. Ether was evaporated off and the residue was fractionated by high performance liquid chromatography on silica gel with a mixture of benzene and AcOEt as an eluent. Concentration of the first fraction afforded 0.12 g of crude III. Recrystallization from petroleum benzin gave 0.062 g (4%) of pure III, mp 115.5°. From the second fraction, 0.363 g of *p*-toluidine was obtained. The total yield of *p*-toluidine, mp 43°, was 0.606 g (65%). Identification of III and *p*-toluidine was carried out by mixed melting point measurement and comparison of their IR spectra with those of corresponding authentic samples.

Hydrolysis of XII in the Presence of AcOH and AcONa——A solution of 0.06 g (0.001 mol) of AcOH and 1.22 g (0.009 mol) of $AcONa\cdot 3H_2O$ in 21 ml of H_2O was added to a solution of 2.64 g (0.01 mol) of XII in 50 ml of EtOH. The reaction solution was heated at 60° for 18.5 hr on a water bath. The reaction mixture was worked up as described in the section on the hydrolysis of I, and 0.245 g (14%) of III, mp 115.5°, and 0.388 g (42%) of *p*-toluidine, mp 43°, were obtained. Each compound was found to be identical with the corresponding authentic sample by mixed melting point measurement and comparison of their IR spectra.

Alkaline Hydrolysis of VII——Ten ml of 1 N NaOH and 72 ml of H_2O were added to a solution of 3.55 g (0.01 mol) of VII in 190 ml of EtOH. The reaction solution was heated at 60° for 9 hr on a water bath, and then concentrated under reduced pressure. From the distillate, 0.58 g (62%) of *p*-toluidine was obtained, mp 43°. Benzene and 7% $NaHCO_3$ were added to the residue. The water layer was neutralized with HCl and extracted with ether. From the ether layer, 0.87 g (71%) of benzoic acid was obtained, mp 122°. The

benzene layer was dried over K_2CO_3, and the solvent was removed under reduced pressure. The residue was dissolved in EtOH, and a solution of EtONa in EtOH was added to the solution. The solution was evaporated to dryness under reduced pressure, and 50 ml of ether was added to the residue. From the ether solution, 0.09 g (4%) of VI was obtained, mp 163°. A 7% aqueous solution of $NaHCO_3$ was added to the residue, and the solution was extracted with ether. The ether layer was dried over Na_2SO_4, and the ether was evaporated off. Recrystallization of the residue from benzene afforded 0.79 g (49%) of VIII, mp 122°. *p*-Toluidine, benzoic acid, VI and VIII were identical with the corresponding authentic samples, on the basis of mixed melting point measurement and comparison of their IR spectra.

Alkaline Hydrolysis of V——Ten ml of 1 N NaOH was added to a solution of 2.92 g (0.01 mol) of V in 150 ml of EtOH, and the reaction solution was allowed to stand for 40 min at room temperature. A yellow crystalline mass gradually precipitated, and was filtered off with suction to give 1.4 g (56%) of VI, mp 163°, which was identical with the authentic sample as judged by mixed melting point measurement and comparison of their IR spectra. The filtrate was concentrated under reduced pressure, and 10 ml of 7% $NaHCO_3$ was added to the residue. The mixture was extracted with benzene, and the water layer was neutralized with HCl then extracted with ether. The ether layer was dried over Na_2SO_4. After removal of the ether, the residue was distilled to give 0.06 g (10%) of AcOH, which was heated with excess aniline at 180° in a sealed tube for 4 hr to give a small amount of acetanilide, mp 114°. Acetanilide thus obtained was found to be identical with an authentic sample by mixed melting point measurement and comparison of their IR spectra.

Hydrolysis of VII in the Presence of AcOH and AcONa——A solution of 0.24 g (0.004 mol) of AcOH and 0.54 g (0.004 mol) of $AcONa \cdot 3H_2O$ in 14 ml of H_2O was added to a solution of 1.42 g (0.004 mol) of VII in 50 ml of dioxane. The reaction solution was allowed to stand overnight at room temperature, and was then heated at 60° for 4 hr on a water bath, and 10 ml of 7% $NaHCO_3$ was added to the solution. The mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in benzene. The benzene solution was washed with H_2O, and dried over K_2CO_3. The solvent was removed under reduced pressure, and the residue was fractionated by high performance liquid chromatography on silica gel with a mixture of benzene and AcOEt as an eluent. From the first fraction, 0.72 g (85%) of *N*-benzoyl-*p*-toluidine was obtained, mp 158°. From the second fraction, 0.13 g (12%) of XIII was obtained, mp 116°. From the last fraction, 0.37 g (57%) of VIII was obtained, mp 122°. *N*-Benzoyl-*p*-toluidine, XIII and VIII were confirmed to be identical with the corresponding authentic samples by mixed melting point measurement and comparison of their IR spectra.

Hydrolysis of V in the Presence of AcOH and AcONa——A solution of 0.40 g (0.0067 mol) of AcOH and 0.90 g (0.0067 mol) of $AcONa \cdot 3H_2O$ in 20 ml of H_2O was added to a solution of 1.95 g (0.0067 mol) of V in 80 ml of dioxane. The reaction solution was allowed to stand for 2 days at room temperature. After addition of 20 ml of 7% $NaHCO_3$, the solution was concentrated under reduced pressure. The residue was dissolved in benzene, and the benzene solution was washed with H_2O, and dried over K_2CO_3. Most of the benzene was removed under reduced pressure, and white crystals were precipitated from the remaining solution. Filtration of the precipitate followed by recrystallization from petroleum benzin gave 0.29 g (29%) of *N*-acetyl-*p*-toluidine. The filtrate was evaporated to dryness under reduced pressure, and the residue was fractionated by high performance liquid chromatography on silica gel with a mixture of benzene and AcOEt as an eluent. From the first fraction, 0.03 g (2%) of XIV was obtained. From the second fraction, 0.80 g (74%) of VIII was obtained, mp 122°. From the last fraction, a trace of VI was obtained, mp 163°. Identification of *N*-acetyl-*p*-toluidine, VIII and VI was carried out by mixed melting point measurement and comparison of the IR spectra with those of the corresponding authentic samples.

Hydrolysis of IX in 80% Dioxane in the Presence of AcOH and AcONa——A solution of 0.3 g (0.005 mol) of AcOH and 0.68 g (0.005 mol) of $AcONa \cdot 3H_2O$ in 13 ml of H_2O was added to a solution of 1.84 g (0.005 mol) of IX in 50 ml of dioxane. The reaction solution was allowed to stand overnight at room temperature, and then heated at 60° for 2 hr on a water bath. A solution of 0.3 g of Na_2CO_3 in 5 ml of H_2O was added to the reaction solution, and the solution was concentrated under reduced pressure to remove most of the dioxane. The remaining aqueous layer was extracted with ether and the ether layer was washed successively with 7% $NaHCO_3$ and H_2O, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was fractionated by silica gel column chromatography with benzene as an eluent. Concentration of the first fraction followed by recrystallization from benzene afforded 0.51 g (48%) of *N*-benzoyl-*p*-toluidine, mp 158°. Concentration of the second fraction followed by recrystallization from petroleum benzin afforded 0.255 g (29%) of III, mp 115.5°. Concentration of the third fraction followed by recrystallization from petroleum ether afforded 0.015 g (1%) of XV, mp 82°. Concentration of the last fraction followed by recrystallization from petroleum benzin afforded a trace of *N*-formyl-*p*-toluidine, mp 53°. *N*-Benzoyl-*p*-toluidine, III, XV and *N*-formyl-*p*-toluidine were identified by comparison with the corresponding authentic samples (mixed melting point measurement and comparison of IR spectra).

Hydrolysis of IX in 80% EtOH in the Presence of AcOH and AcONa——A solution of 0.60 g (0.01 mol) of AcOH and 1.38 g (0.01 mol) of $AcONa \cdot 3H_2O$ in 20 ml of H_2O was added to a solution of 3.69 g (0.01 mol) of IX in 80 ml of EtOH. The reaction solution was allowed to stand overnight at room temperature, and was then heated at 60° for 4 hr on a water bath. After addition of 0.8 g of $NaHCO_3$, the solution was evapo-

rated to dryness under reduced pressure. The distillate, after being made acidic by the addition of HCl, was evaporated to dryness under reduced pressure. A small amount of *p*-toluidine, mp 43°, was obtained from the residue. On addition of 10 ml of benzene to the former residue, white crystals were deposited. The crystals were filtered off with suction, and recrystallized from benzene to yield 0.82 g of *N*-benzoyl-*p*-toluidine, mp 158°. The filtrate was evaporated to dryness under reduced pressure, and the residue was fractionated by column chromatography on silica gel with a mixture of benzene and AcOEt as an eluent. Concentration of the first fraction followed by recrystallization from benzene afforded 0.39 g of *N*-benzoyl-*p*-toluidine, mp 158°. The total yield of *N*-benzoyl-*p*-toluidine was 1.21 g (57%). Concentration of the second fraction, followed by recrystallization from petroleum benzin afforded 0.25 g (14%) of III, mp 115.5°. Evaporation of the last fraction followed by recrystallization from petroleum benzin afforded 0.03 g (2%) of II, mp 91°. *Anal.* Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.60; H, 7.42; N, 8.01. *N*-Benzoyl-*p*-toluidine and III were identified by comparison with the corresponding authentic samples (mixed melting point measurement and comparison of IR spectra).

References and Notes

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8) Besides these signals, other small signals due to the 1- and 2-position were observed at δ 8.12 ppm (doublet, $J=15$ Hz) and 5.22 ppm (doublet, $J=15$ Hz), respectively, suggesting that IX exists as a mixture of two conformational isomers in deuterochloroform.
9) M. Julia (*Ann. Chim.*, [**12**], 594 (1950) [*C.A.*, **46**, 7035 (1952)]) reported that the melting point of III is 111—112°.