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Preparation and Cyclodehydration of β-Arylaminocrotonaldehyde

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β-Arylaminocrotonaldehydes (**3**) were prepared by alkaline hydrolysis of 1-arylamino-3-arylimino-1-butenes (**2**). On treatment with sulfuric acid, β-anilinocrotonaldehyde (**3b**) and *p*-methyl- (**3a**), *m*-chloro- (**3c**), and *p*-chloro- (**3d**) derivatives were cyclodehydrated to give the corresponding quinaldines in quantitative yields. The protonation of **3** was proved to take place at the oxygen atom on the basis of spectral evidence.

The mechanism of the cyclodehydration is discussed.

Keywords——Combes reaction; cyclodehydration; hydrolysis; β-arylaminocrotonaldehyde; 1-arylamino-3-arylimino-1-butene; quinaldine derivative; protonation

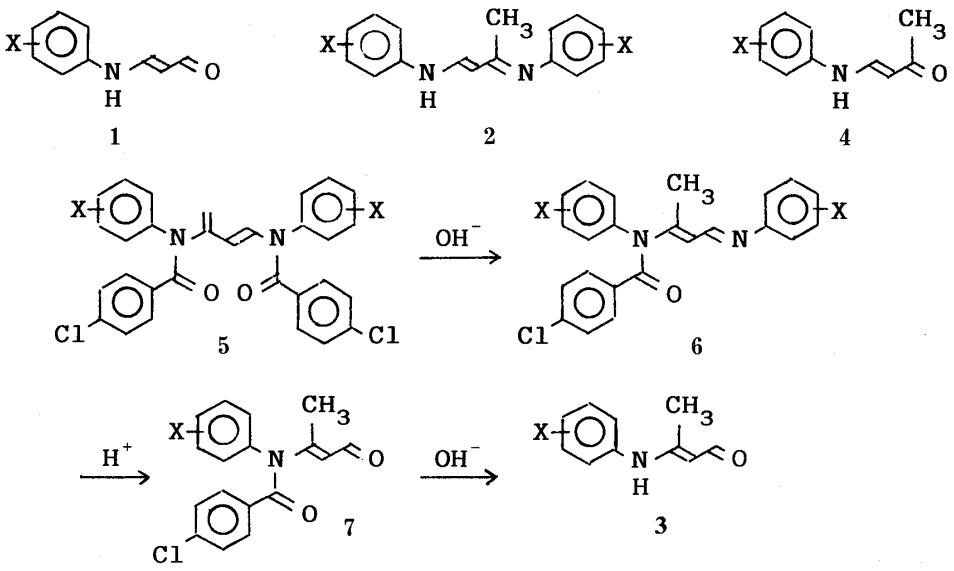
In a previous paper[1] we reported a kinetic study of the cyclodehydration of β-(*p*-methylphenylamino)acrolein (**1a**) in sulfuric acid (Combes reaction). β-(*p*-Chloroanilino)acrolein (**1d**) and β-anilinoacrolein (**1b**) were not cyclodehydrated to give quinolines, and the latter was sulfonated at *p*-position in sulfuric acid.[2] In order to examine the influence of aryl substituents on the rate of cyclodehydration, we attempted to prepare β-arylaminocrotonaldehydes, which are expected to be cyclodehydrated to give quinaldines more readily than β-arylaminoacroleins (**1**).

The hydrolysis of 1-(*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-butene (**2a**) in the presence of acetic acid and sodium acetate did not give the desired compound, β-(*p*-methylphenylamino)crotonaldehyde (**3a**), but gave 4-(*p*-methylphenylamino)-3-buten-2-one (**4a**).[3] The preparation of **3a** was achieved by the following route[4]: β-[*N*-(*p*-Chlorobenzoyl)-*p*-methylphenylamino]crotonaldehyde (**7a**) was prepared by the alkaline hydrolysis of 1,3-bis[*N*-(*p*-chlorobenzoyl)-*p*-methylphenylamino]-1,3-butadiene (**5a**) followed by acid hydrolysis of the resulting 3-[*N*-(*p*-chlorobenzoyl)-*p*-methylphenylamino]-1-(*p*-methylphenylimino)-2-butene (**6a**), and the removal of the *p*-chlorobenzoyl group of **7a** by alkaline hydrolysis gave **3a** (Chart 1).

In this paper we wish to report the preparation and cyclodehydration of β-arylaminocrotonaldehydes (**3**).

In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of the crude product of alkaline hydrolysis of 1,3-bis[*N*-(*p*-chlorobenzoyl)-*p*-chloroanilino]-1,3-butadiene (**5d**), weak signals of 3-[*N*-(*p*-chlorobenzoyl)-*p*-chlorophenylamino]-1-(*p*-chlorophenylimino)-2-butene (**6d**) were observed at δ 6.45 (dq, $J_d = 9$ Hz and $J_q = 0.5$ Hz, 2-position), 6.15 (dq, $J_d = 9$ Hz and $J_q = 0.5$ Hz, 2-position of conformational isomer), 8.48 (d, $J = 9$ Hz, 1-position) and 8.32 (d, $J = 9$ Hz, 1-position of conformational isomer) among other unidentifiable signals. It appears that a small amount of **6d** was formed on alkaline hydrolysis of **5d** together with larger amounts of unidentifiable by-products, and **6d** could not be isolated from the reaction mixture. The preparative route[4] for **3a** is, therefore, unsuitable for general application to the preparation of derivatives of **3**.

Hydrolysis of **2a** was reexamined. In 90% ethanol, **2a** was heated at 80 °C in the presence



X

p-CH_3	:	**1a**, **2a**, **3a**, **4a**, **5a**, **6a**, **7a**
H	:	**1b**, **2b**, **3b**, **4b**
m-Cl	:	**2c**, **3c**
p-Cl	:	**1d**, **2d**, **3d**, **4d**, **5d**, **6d**

Chart 1

of a 3-fold molar excess of acetic acid and sodium acetate for 1.5 h. Analysis of the ^{1}H-NMR spectrum (deuterochloroform) of the crude product[5] showed that the mixture consisted of **2a** (0.38),[6] **3a** (0.28), **4a** (0.35), *p*-toluidine (0.61) and 4,4-diethoxy-2-butanone (**8**, 0.15). The latter was characterized by the signals at δ 1.18 (t, $J=7$ Hz, methyl of ethoxyl group), 2.16 (s, 1-position), 2.75 (d, $J=6$ Hz, 3-position) and 4.89 (t, $J=6$ Hz, 4-position), and the methylene signal of the ethoxyl group was observed as a set of double quartets at δ 3.52 and 3.65. The signal peaks observed were as follows (400 MHz, digital resolution, 0.18 Hz); δ 3.480, 3.497, 3.502, 3.515, 3.520, 3.533, 3.538, 3.556, 3.613, 3.631, 3.636, 3.649, 3.654, 3.666, 3.672 and 3.689. The methylene signal of aldehyde diethyl acetal (except for ethylal) shows a complex pattern owing to the nonequivalence of the two protons of each methylene group.[7] Treatment of **3a** under the same conditions gave a mixture of **2a** (0.03), **3a** (0.63), **4a** (0.25), *p*-toluidine (0.05) and **8** (0.02), while **4a** showed no change on the same treatment.

There are two possible courses of hydrolysis of **2**. One of them is at the 1-position to give **3**, and the other is at the 3-position to give 4-arylamino-3-buten-2-ones (**4**). From the results of the above experiment it is concluded that the hydrolysis of **2a** under acidic conditions occurs at the 1-position to a considerable extent, and the resulting **3a** is further hydrolyzed or alcoholyzed to give *p*-toluidine and acetoacetaldehyde or **8**, then *p*-toluidine recombines with acetoacetaldehyde to give **4a** irreversibly. As the result, hydrolysis of **2a** under acidic conditions gave mainly **4a** (Chart 2).

In 90% ethanol, **2a** was heated at 80 °C in the presence of a 2-fold molar excess of sodium hydroxide for 1.5 h. The resulting crude product consisted of **2a** (0.64), **3a** (0.27), **4a** (0.04) and *p*-toluidine (0.42). No signals due to **8** could be detected in the ^{1}H-NMR spectrum. The treatment of **3a** under the same conditions gave a mixture which consisted of **2a** (0.08), **3a** (0.73) and *p*-toluidine (0.10). No signals due to **4a** and **8** could be detected in the ^{1}H-NMR spectrum. The results mean that the alkaline hydrolysis of **2a** occurs mainly at the 1-position to give **3a**, and **3a** formed is further hydrolyzed to give acetoacetaldehyde and *p*-toluidine to a small extent; further, the resulting *p*-toluidine combines with **3a** to give **2a** but not with

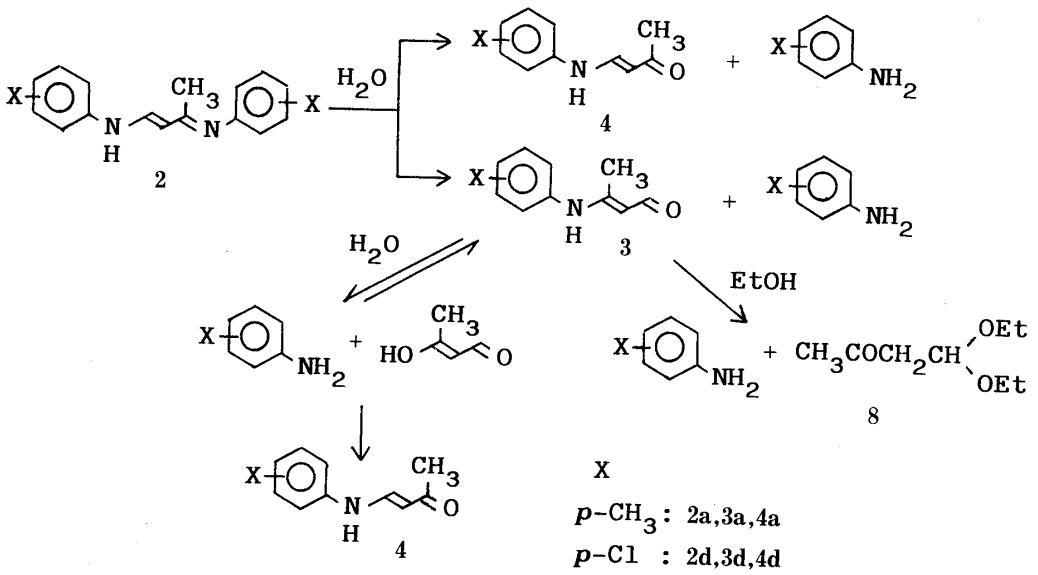


Chart 2

acetoacetaldehyde to give **4a**.

Hydrochloride of **2a** was heated at 80 °C in 80% aqueous ethanolic solution in the presence of a 3-fold molar excess of sodium hydroxide for 1.5 h. The crude product was purified by column chromatography (alumina, benzene–methanol) followed by preparative thin layer chromatography (PTLC, silica-gel, benzene–ethyl acetate) to give **3a** in 23% yield. The hydrochlorides of 1-phenylamino-3-phenylimino-1-butene (**2b**), 1-(*m*-chlorophenylamino)-3-(*m*-chlorophenylimino)-1-butene (**2c**) and 1-(*p*-chlorophenylamino)-3-(*p*-chlorophenylimino)-1-butene (**2d**) were treated in the same manner to give β-anilinocrotonaldehyde (**3b**, 14%), β-(*m*-chloroanilino)crotonaldehyde (**3c**, 34%) and β-(*p*-chloroanilino)-crotonaldehyde (**3d**, 24%), respectively.

The composition of the crude products formed on hydrolysis of **2d** and of **3d** was evaluated from the ^{1}H-NMR spectra. On heating for 2 h under the same conditions as used for the hydrolysis of **2a** in the presence of acetic acid and sodium acetate, **2d** gave a product which consisted of **2d** (0.07), **3d** (0.26), 4-(*p*-chloroanilino)-3-buten-2-one (**4d**, 0.48), *p*-chloroaniline (1.12) and **8** (0.11). Under the same conditions **3d** gave a product which consisted of **2d** (0.07), **3d** (0.36), **4d** (0.39), *p*-chloroaniline (0.11) and **8** (0.02). The results were similar to those of the hydrolysis of **2a** and of **3a** in the presence of acetic acid and sodium acetate. On the other hand, alkaline hydrolysis of **2d** gave somewhat different results from those of the same reaction of **2a**. On heating for 2 h under the same conditions as used for the alkaline hydrolysis of **2a**, **2d** gave a product which consisted of **2d** (0.49), **3d** (0.42) and *p*-chloroaniline (0.60). No signals due to **4d** could be detected in the ^{1}H-NMR spectrum of the product. This means that the hydrolysis of **2d** under alkaline conditions occurs predominantly at the 1-position to give **3d**. The alkaline hydrolysis of **3d** under the same conditions gave a product which consisted of **2d** (0.13), **3d** (0.63) and *p*-chloroaniline (0.12).

Compound **3a** was cyclodehydrated to give 2,6-dimethylquinoline in quantitative yield on standing in 80.1% sulfuric acid solution at room temperature for 2 d. Compounds **3b**, **3c** and **3d** were similarly treated in sulfuric acid of appropriate concentration to give quinaldine, a mixture of 5- and 7-chloroquinaldines and 6-chloroquinaldine in quantitative yields, respectively. The product derived from **3c** was found by high performance liquid chromatography (HPLC) to be a mixture of 5- and 7-chloroquinaldines in a ratio of 11 : 89 (Chart 3).

Our previous study[1)] revealed that the rate of cyclodehydration of 4-(*p*-methylphenylamino)-3-penten-2-one (**9a**) in sulfuric acid was forty times higher than that of **1a**.

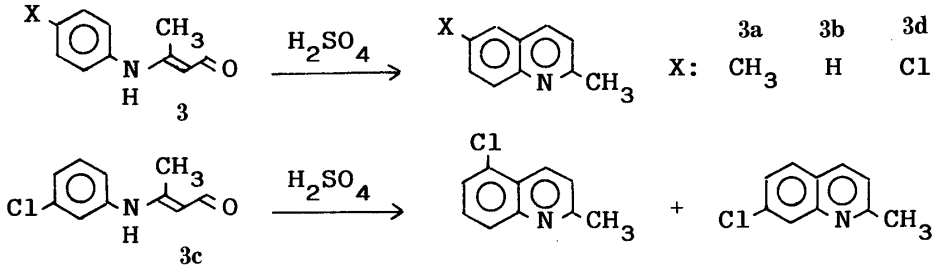


Chart 3

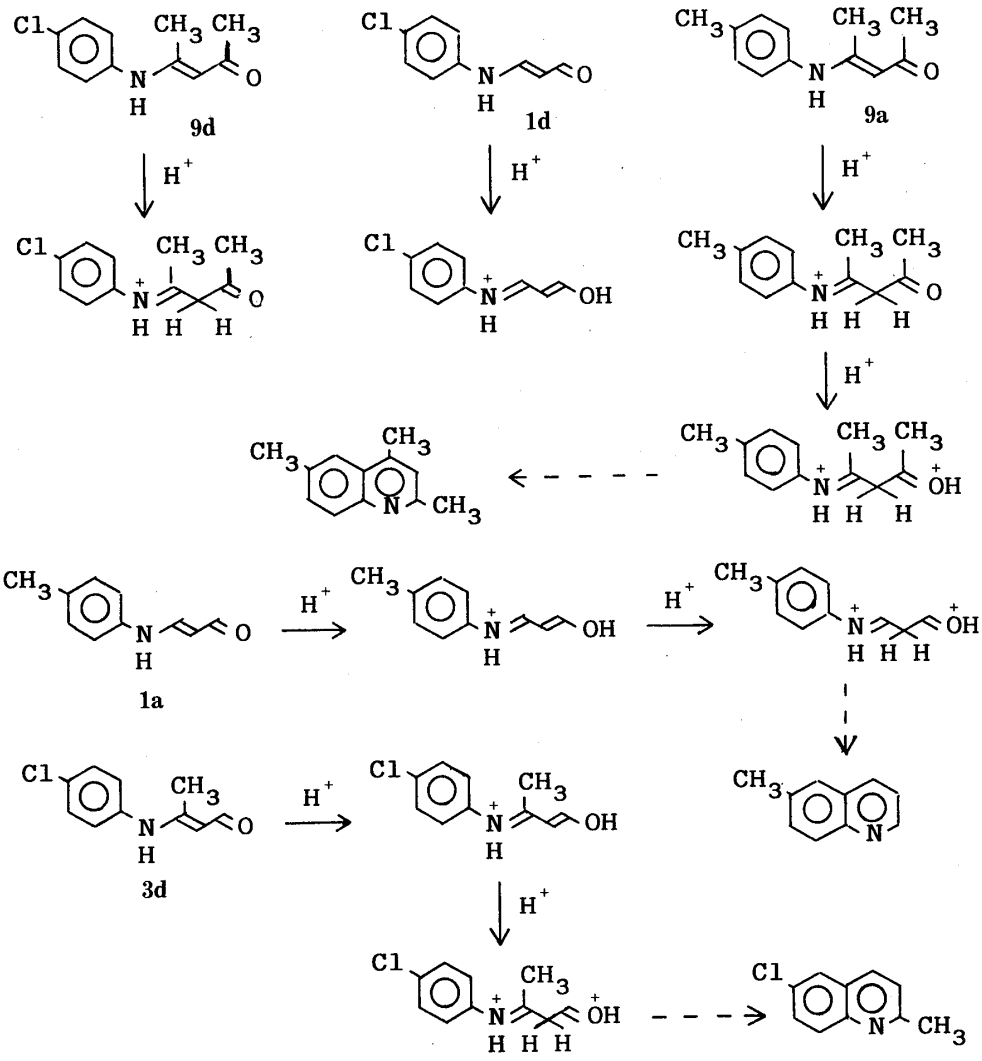


Chart 4

We presumed that the difference of reactivity in the cyclodehydrations of **9a** and **1a** is attributable to the difference in the position at which protonation takes place.[8] The protonations of 4-(*p*-chloroanilino)-3-penten-2-one (**9d**) and of **1d** were found to take place at the 3-position of **9d** and at the oxygen atom of **1d** on the basis of a comparison of their ^{1}H-NMR spectra, and the above conclusion was supported by the ultraviolet absorption (UV) spectra of **9a** and of **1a**.[9] The cyclodehydration in the Combes reaction proceeds through a diprotonated species,[10] and monoprotonated **1a** is expected to resist diprotonation because of its resonance stability while monoprotonated **9a** is diprotonated more easily.

Compound **3d** was cyclodehydrated to give 6-chloroquinaldine in sulfuric acid while **9d**

resisted cyclodehydration under the same conditions.[11] β-Arylaminocrotonaldehyde is, therefore, more reactive in cyclodehydration than 4-arylamino-3-penten-2-one.

The ^{1}H-NMR spectrum (75.3% sulfuric acid) of **3d** showed signals at δ 3.34 (s, methyl group), 6.64 (d, J=12 Hz, α-position) and 8.88 (d, J=12 Hz, formyl group), as well as weak signals due to a conformational isomer at δ 3.08 (s, methyl group), 6.90 (d, J=12 Hz, α-position) and 8.84 (d, J=12 Hz, formyl group). The relative integrated value of each signal showed that the formyl group, α-position and methyl group contained hydrogen atoms in a ratio of 1 : 1 : 3. The protonation of **3d** in sulfuric acid was thus proved to take place not at the α-position but at the oxygen atom (Chart 4).

The UV spectrum (63.2% sulfuric acid) of **3a** showed an absorption maximum at 292 nm (ε=15390). Hypsochromic shift and hypochromic change as compared with the spectrum of monoprotonated **1a** suggests that the conjugation system in the monoprotonated β-arylaminocrotonaldehyde is partially destroyed by the obstruction of coplanarity of the system due to the steric hindrance of the β-methyl group. The monoprotonated β-arylaminocrotonaldehyde is diprotonated more easily than monoprotonated β-arylaminoacrolein in sulfuric acid solution. Generally, aldehydes are more reactive than ketones in carbonyl addition reaction. As might be expected, β-arylaminocrotonaldehyde is the most reactive in cyclodehydration among the systems examined.

Experimental

All melting points are uncorrected. The UV spectra were measured on a Hitachi spectrophotometer, model 139, and the ^{1}H-NMR spectra were recorded on JEOL PMX 60 and JEOL GX 400 NMR spectrometers with tetramethylsilane as an internal or external reference. The following abbreviations are used: singlet (s), doublet (d), double doublet (dd), double quartet (dq), and triplet (t). Preparative HPLC and analysis by HPLC were carried out with a Waters liquid chromatograph system 500 and a Waters liquid chromatograph ALC/GPC 204A compact type, respectively.

Compound **2a**,[3] its hydrochloride,[3] hydrochloride of **2b**,[12] and **4a**[3] were prepared according to the cited references. Compound **4d** was prepared as described by Thielepape[13] and it melted at 121 °C. Böhme[14] reported that the melting point of **4d** is 115 °C.

The samples of *N*-acetyl-*m*-chloroaniline, *N*-formyl-*p*-chloroaniline, *p*-toluidine, *p*-chloroaniline, acetanilide, *N*-formyl-*p*-toluidine, 6-chloroquinaldine, 2,6-dimethylquinoline described in this section were identical with authentic samples on the basis of mixed melting point measurement and comparison of their infrared absorption (IR) spectra. The samples of *N*-formylaniline and quinaldine described in this section were identical with authentic samples on the basis of comparison of their IR spectra.

1-(*m*-Chlorophenylamino)-3-(*m*-chlorophenylimino)-1-butene (2c) Hydrochloride——A solution of 13.79 g of β-chlorocrotonaldehyde[12] in 50 ml of a mixture of benzene–EtOH (2 : 1) was added slowly to a solution of *m*-chloroaniline (33.63 g) in 200 ml of the same solvent under ice cooling. The mixture was allowed to stand in a refrigerator for 1 d. The precipitate was collected to give 44.78 g (98%) of HCl salt of **2c**. mp 191 °C (dec.). *Anal.* Calcd for $C_{16}H_{14}Cl_2N_2 \cdot HCl \cdot 1/4H_2O$: C, 55.51; H, 4.51; N, 8.09. Found: C, 55.69; H, 4.36; N, 7.91. ^{1}H-NMR (CD_3SOCD_3–D_2O) δ: 2.75 (3H, s, CH_3), 6.10 (1H, d, J=12 Hz, 2-position) and 8.83 (1H, d, J=12 Hz, 1-position).

1-(*p*-Chlorophenylamino)-3-(*p*-chlorophenylimino)-1-butene (2d)——A solution of 13.79 g of β-chlorocrotonaldehyde[12] in 50 ml of a mixture of benzene–EtOH (2 : 1) was added to a solution of 33.63 g of *p*-chloroaniline in 200 ml of the same solvent under ice cooling. The mixture was allowed to stand in a refrigerator for 1 d. The precipitate was collected to give 48.81 g (97%) of HCl salt of **2d**. mp 196 °C (dec.). *Anal.* Calcd for $C_{16}H_{14}Cl_2N_2 \cdot HCl \cdot 1/2C_6H_6$: C, 59.94; H, 4.77; N, 7.36. Found: C, 59.47; H, 4.78; N, 7.13. ^{1}H-NMR (CD_3OD) δ: 2.80 (3H, s, CH_3), 6.17 (1H, d, J=12 Hz, 2-position) and 8.83 (1H, d, J=12 Hz, 1-position).

A mixture of HCl salt of **2d** (39.39 g), 10% Na_2CO_3 (700 ml) and benzene (1300 ml) was stirred for 3 h. The benzene layer was dried over K_2CO_3, and concentrated under reduced pressure. The residue was recrystallized from petroleum benzin to give 30.11 g (95%) of **2d**. mp 104 °C. *Anal.* Calcd for $C_{16}H_{14}Cl_2N_2$: C, 62.97; H, 4.62; N, 9.18. Found: C, 62.62; H, 4.50; N, 8.92. ^{1}H-NMR ($CDCl_3$) δ: 1.95 (3H, s, CH_3), 5.01 (1H, d, J=8 Hz, 2-position) and 7.17 (1H, d, J=8 Hz, 1-position).

1,3-Bis[*N*-(*p*-chlorobenzoyl)-*p*-chloroanilino]-1,3-butadiene (5d)——A solution of *p*-chlorobenzoyl chloride (15.02 g) in 100 ml of CH_2Cl_2 was added to a solution of **2d** (23.81 g) and Et_3N (15.79 g) in 300 ml of CH_2Cl_2 under ice cooling. The mixture was allowed to stand for 15 min 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 was purified by reprecipitation from CH_2Cl_2 solution by addition of petroleum ether to give 31.96 g (92%) of 1-[*N*-(*p*-chlorobenzoyl)-*p*-chlorophenylamino]-3-(*p*-chlorophenylimino)-1-butene. mp 155 °C. *Anal.* Calcd for $C_{23}H_{17}Cl_3N_2O \cdot 1/2H_2O$: C, 61.01; H, 4.01; N, 6.19. Found: C, 61.05; H, 3.68; N, 6.07. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s, CH_3), 5.60 (1H, d, J= 15 Hz, 2-position) and 8.33 (1H, d, J=15 Hz, 1-position). Among these signals, weak signals of a conformational isomer were observed at δ 2.37 (s, CH_3), 5.20 (d, J=15 Hz, 2-position) and 8.20 (d, J=15 Hz, 1-position).

A solution of *p*-chlorobenzoyl chloride (1.93 g) in 5 ml of benzene was added slowly to a solution of 1-[*N*-(*p*-chlorobenzoyl)-*p*-chlorophenylamino]-3-(*p*-chlorophenylimino)-1-butene (4.44 g) and Et_3N (3.03 g) in 33 ml of benzene under ice cooling. The mixture was refluxed for 2 h on an oil bath with stirring. The deposited crystals of $Et_3N \cdot HCl$ were filtered off with suction. The filtrate was washed with 7% $NaHCO_3$, dried over K_2CO_3, and concentrated under reduced pressure. The residue was recrystallized from MeOH to give 4.73 g (81%) of **5d**. mp 188 °C. *Anal.* Calcd for $C_{30}H_{20}Cl_4N_2O_2$: C, 61.88; H, 3.46; N, 4.81. Found: C, 61.73; H, 3.44; N, 4.79. ^{1}H-NMR ($CDCl_3$) δ: 4.83 (1H, s, 4-position), 5.08 (1H, s, 4-position), 5.25 (1H, d, J=15 Hz, 2-position) and 7.67 (1H, d, J= 15 Hz, 1-position).

^{1}H-NMR Analysis of Hydrolysis Products of 2a, 3a, 4a, 2d, 3d and 4d——Hydrolysis of **2a** in the Presence of AcOH and AcONa: A solution of AcOH (0.18 g) and AcONa·$3H_2O$ (0.41 g) in H_2O (1.41 g) was added to a solution of **2a** (0.26 g) in 18 ml of EtOH. The mixture was heated at 80 °C for 1.5 h on a water bath, then 10 ml of 7% $NaHCO_3$ was added, and the mixture was concentrated under reduced pressure. The remaining liquid was extracted with ether, and the ether layer was dried over Na_2SO_4, and concentrated under reduced pressure. A small amount of $CDCl_3$ was added to the residue and the mixture was concentrated under reduced pressure. This treatment was repeated three times, then the residue was dissolved in $CDCl_3$ for measurement of the ^{1}H-NMR spectrum.

Hydrolysis of **2d** in the Presence of AcOH and AcONa: Compound **2d** (0.30 g) was heated for 2 h under the same conditions as described for the hydrolysis of **2a**, and the reaction solution was treated as described above.

Hydrolysis of **3a** in the Presence of AcOH and AcONa: A solution (0.2 g) of AcOH (0.18 g) and AcONa·$3H_2O$ (0.41 g) in H_2O (1.41 g) was added to a solution of **3a** (0.018 g) in 1.8 ml of EtOH. The mixture was heated at 80 °C for 1.5 h on a water bath. Two ml of 7% $NaHCO_3$ was added to the reaction solution, and the mixture was concentrated under reduced pressure. The remaining liquid was treated in the manner described above.

Hydrolysis of **4a** in the Presence of AcOH and AcONa: Compound **4a** (0.018 g) was treated in the manner as described for the hydrolysis of **3a**.

Hydrolysis of **3d** in the Presence of AcOH and AcONa: Compound **3d** (0.019 g) was heated for 2 h under the same conditions as described for the hydrolysis of **3a**, and the reaction solution was treated in the manner described above.

Hydrolysis of **4d** in the Presence of AcOH and AcONa: Compound **4d** (0.019 g) was treated in the manner as described for the hydrolysis of **3d**.

Alkaline Hydrolysis of **2a**: A solution (1.0 g) of NaOH (0.8 g) in H_2O (9.2 g) was added to a solution of **2a**(0.26 g) in 18 ml of EtOH. The mixture was heated at 80 °C for 1.5 h on a water bath. The reaction solution was treated in the manner as described for the hydrolysis of **2a** in the presence of AcOH and AcONa.

Alkaline Hydrolysis of **2d**: Compound **2d** (0.30 g) was heated for 2 h under the same conditions as described for the alkaline hydrolysis of **2a**, and the reaction solution was treated in the manner described above.

Alkaline Hydrolysis of **3a**: A solution (0.2 g) of NaOH (0.16 g) in H_2O (3.4 g) was added to a solution of **3a** (0.0175 g) in 1.8 ml of EtOH. The mixture was heated at 80 °C for 1.5 h on a water bath. Two ml of 7% $NaHCO_3$ was added to the reaction solution, and the mixture was treated in the manner described above.

Alkaline Hydrolysis of **3d**: Compound **3d** (0.0196 g) was heated for 2 h under the same conditions as described for the hydrolysis of **3a**, and the reaction solution was treated in the manner described above.

The ^{1}H-NMR signals of **2a**, **2d**, **3a**, **3d**, **4a**, **4d**, *p*-toluidine and *p*-chloroaniline used for analysis of hydrolysis products were as follows. **2a**: δ 1.95 (3H, s, CH_3), 2.29 (3H, s, CH_3), 2.34 (3H, s, CH_3), 4.96 (1H, d, J=7.5 Hz, 2-position), 6.80 (2H, d, J=8 Hz, aromatic ring), 6.88 (2H, d, J=8 Hz, aromatic ring), 7.07 (2H, d, J=8 Hz, aromatic ring), 7.14 (2H, d, J=8 Hz, aromatic ring) and 7.27 (1H, d, J=7.5 Hz, 1-position). **3a**: δ 1.99 (3H, s, CH_3), 2.35 (3H, s, CH_3), 5.12 (1H, d, J=2.5 Hz, α-position), 7.02 (2H, d, J=8 Hz, aromatic ring), 7.16 (2H, d, J=8 Hz, aromatic ring) and 9.05 (1H, d, J=2.5 Hz, CHO). **4a**: δ 2.14 (3H, s, CH_3), 2.30 (3H, s, CH_3), 5.26 (1H, d, J=7.5 Hz, 3-position), 6.92 (2H, d, J=8.5 Hz, aromatic ring), 7.11 (2H, d, J=8.5 Hz, aromatic ring) and 7.19 (1H, dd, J=7.5 and 12.5 Hz, 4-position). *p*-Toluidine: δ 6.61 (2H, d, J=8 Hz, aromatic ring) and 6.96 (2H, d, J=8 Hz, aromatic ring). **2d**: δ 1.93 (3H, s, CH_3), 5.01 (1H, d, J=8 Hz, 2-position), 6.79 (2H, d, J=8.5 Hz, aromatic ring), 6.85 (2H, d, J=9 Hz, aromatic ring), 7.17 (1H, d, J=8 Hz, 1-position), 7.22 (2H, d, J=9 Hz, aromatic ring) and 7.28 (2H, d, J=8.5 Hz, aromatic ring). **3d**: δ 2.01 (3H, s, CH_3), 5.18 (1H, d, J=2.5 Hz, α-position), 7.07 (2H, d, J=9 Hz, aromatic ring), 7.33 (2H, d, J=9 Hz, aromatic ring) and 9.07 (1H, d, J=2.5 Hz, CHO). **4d**: δ 2.16 (3H, s, CH_3), 5.32 (1H, d, J=8 Hz, 3-position), 6.95 (2H, d, J=9 Hz, aromatic ring), 7.14 (1H, dd, J=8 and 12 Hz, 4-position) and 7.27 (2H, d, J=9 Hz, aromatic ring). *p*-Chloroaniline: δ 6.60 (2H, d, J=9 Hz, aromatic ring) and 7.09 (2H, d, J=9 Hz, aromatic ring).

***β*-(*p*-Methylphenylamino)crotonaldehyde (3a)**——A solution of NaOH (1.2 g) in 18 ml of H_2O was added to a solution of hydrochloride of **2a** (3.49 g) in 72 ml of EtOH. The mixture was heated at 80 °C for 1.5 h on a water bath, and 250 ml of 7% $NaHCO_3$ was added to the mixture. The mixture was distilled under reduced pressure. The distillate

was treated as usual to give 0.68 g of *p*-toluidine. The remaining liquid was extracted with ether, and the ether layer was dried over $MgSO_4$, then concentrated under reduced pressure. The residue was subjected to column chromatography (Al_2O_3, benzene–MeOH) followed by PTLC (silica-gel, benzene–AcOEt) to give 0.41 g (23%) of **3a**, 10 mg of **4a**, 15 mg of *N*-formyl-*p*-toluidine and 0.64 g of **2a**. Compound **3a** was identical with authentic sample[4] on the basis of mixed melting point measurement and comparison of the IR spectra.

β-Anilinocrotonaldehyde (3b)——A solution of NaOH (0.8 g) in 10 ml of H_2O was added to a solution of hydrochloride of **2b** (2.73 g) in 40 ml of EtOH. The mixture was heated at 80 °C for 3.5 h on a water bath, and 250 ml of 7% $NaHCO_3$ was added. The whole was distilled under reduced pressure, and the distillate was treated as usual to give 0.50 g of aniline, which was identified as the *N*-acetyl derivative. The remaining liquid was extracted with ether. The ether layer was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (Al_2O_3, benzene–MeOH) followed by PTLC (silica-gel, benzene–AcOEt) to give 0.23 g (14%) of **3b**, mp 99 °C, 15 mg of **4b**, small amounts of acetanilide and *N*-formylaniline and 0.55 g of **2b**. *Anal.* Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.82; H, 6.98; N, 8.59. ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, CH_3), 5.25 (1H, d, $J=3$ Hz, α-position) and 9.22 (1H, d, $J=3$ Hz, CHO).

β-(*m*-Chloroanilino)crotonaldehyde (3c)——A solution of NaOH (0.6 g) in 20 ml of H_2O was added to a solution of hydrochloride of **2c** (1.73 g) in 80 ml of EtOH. The mixture was heated at 80 °C for 2 h on a water bath, and 125 ml of 7% $NaHCO_3$ was added. The whole was distilled under reduced pressure, and the distillate was treated as usual to give 0.29 g of *m*-chloroaniline, which was identified as the *N*-acetyl derivative. The remaining liquid was extracted with ether. The ether layer was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (Al_2O_3, benzene–MeOH) followed by PTLC (silica-gel, benzene–AcOEt) to give 0.33 g (34%) of **3c**, mp 76 °C, and 0.35 g of **2c**. *Anal.* Calcd for $C_{10}H_{10}ClNO$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.12; H, 5.02; N, 7.02. ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, CH_3), 5.28 (1H, d, $J=3$ Hz, α-position) and 9.25 (1H, d, $J=3$ Hz, CHO).

β-(*p*-Chloroanilino)crotonaldehyde (3d)——A solution of NaOH (0.6 g) in 10 ml of H_2O was added to a solution of hydrochloride of **2d** (2.02 g) in 40 ml of EtOH. The mixture was heated at 80 °C for 2 h on a water bath, and 125 ml of 7% $NaHCO_3$ was added. The whole was distilled under reduced pressure, and the distillate was treated as usual to give 0.67 g of *p*-chloroaniline. The remaining liquid was extracted with ether. The ether layer was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (Al_2O_3, benzene–MeOH) followed by PTLC (silica-gel, benzene–AcOEt) to give 0.25 g of **3d**, mp 95.5 °C, 20 mg of *N*-formyl-*p*-chloroaniline and a small amount of *p*-chloroaniline. *Anal.* Calcd for $C_{10}H_{10}ClNO$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.45; H, 5.04; N, 7.00.

Cyclodehydration of 3a—d——Compound **3a** (0.0015 mol) was dissolved in 1.5 ml of 80.1% H_2SO_4. The reaction solution was allowed to stand for 2 d at room temperature. The mixture was treated as usual to give 0.214 g (91%) of 2,6-dimethylquinoline. Compounds **3b—d** were treated with H_2SO_4 at the appropriate concentration under the same conditions to give the corresponding quinaldines. The concentration (%) of H_2SO_4 used and yield (%) of each quinaldine derivative were as follows. **3b**: 84.0; 89. **3c**: 87.0; 93. **3d**: 96.2; 92.

The product of cyclodehydration of **3c** was analyzed by HPLC in the following manner. The authentic samples of 5- and 7-chloroquinaldines were prepared by a modification of Spivey and Curd's method.[15] A mixture of 18.0 g of *m*-chloroaniline, 71 ml of 72.2% H_2SO_4 and 35 g of sodium *m*-nitrobenzenesulfonate was heated at 120—130 °C. Paraldehyde (22.5 ml) was added to the hot mixture over a period of 20 min with stirring. The mixture was refluxed for an additional 1.5 h, and treated as usual to give a mixture of 5- and 7-chloroquinaldines. Recrystallization of the mixture from petroleum ether gave 8.64 g of 7-chloroquinaldine. mp 77 °C.[16] The mother liquor was concentrated under reduced pressure. The residue (3.10 g) was subjected to preparative HPLC (Prep PAK-500/C18, 35% 0.02 M K_2HPO_4–65% MeOH) to give 0.15 g of 7-chloroquinaldine and 0.79 g of crude 5-chloroquinaldine. Recrystallization of the latter from petroleum ether gave 0.28 g of pure 5-chloroquinaldine trihydrate. mp 50 °C.[16]

The cyclodehydration product of **3c** was proved to be a mixture of 5- and 7-chloroquinaldines in a ratio of 11 : 89 by HPLC (μ-BONDAPAK C18, 35% 0.02 M K_2HPO_4–65% MeOH) using the above samples as standards.

References and Notes

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9) The signal of the 3-position of **9d** was observed at δ 4.42 (2H, br s) and that of the α-position of **1d** was observed at δ 6.30 (1H, t, J = 11 Hz) in the ^{1}H-NMR spectra (83% H_2SO_4). The absorption maxima in the UV spectra of **9a** and of **1a** were observed at 288 nm (ε = 5250) in 75.7% sulfuric acid solution and at 332 nm (ε = 22030) in 81.3% sulfuric acid solution, respectively.[8)]
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16) Spivey and Curd[15)] reported that the melting point of 7-chloroquinaldine is 77—78 °C and that of 5-chloroquinaldine trihydrate is 52—53 °C.