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A Kinetic Study of Formation of β-Arylaminoacrolein Derivatives from β-Ethoxyacrolein and Aromatic Primary Amines

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Formation of β-arylaminoacrolein from β-ethoxyacrolein (I) and arylamine was studied kinetically. Hammett plot for second order rate constants gave a good linear line with ρ value of -2.63. Neither triethylamine nor acetic acid acted as an effective catalyst for the reaction. In the presence of acetic acid a remarkable amount of malonaldehyde dianil formed as a by-product.

Reaction mechanism was discussed.

Keywords——kinetic study; aminolysis; Hammett plot; β-(*p*-toluidino)-acrolein; malonaldehyde dianil; β-ethoxyacrolein; conformational isomerism

In the previous paper[2] we have reported the synthesis of β-arylaminoacrolein derivatives from β-ethoxyacrolein (I) and primary arylamines. In the reaction of I and *p*-nitroaniline, however, the latter was recovered unchanged, and β-(4-pyridylamino)-acrolein could not be isolated from the reaction mixture of I and 4-aminopyridine.[3]

A kinetic study by Bunnett and Davis[4] revealed that the aminolysis reaction of ethyl formate by *n*-butylamine is catalyzed by *n*-butylamine itself, and that aminolysis reaction of methyl benzoate by *n*-butylamine is markedly accelerated by adding sodium methoxide. These facts imply that the reaction of arylamine and I, a vinylog of ester, is accelerated by adding the base stronger than arylamine. In the presence of triethylamine, however, *p*-nitroaniline was recovered unchanged from the reaction mixture of *p*-nitroaniline and I, and β-(*p*-nitroanilino)-acrolein could not be isolated from the reaction mixture of *p*-nitroaniline and I in methanolic sodium methoxide solution.

Kinetic study of the formation of β-arylaminoacrolein from I and arylamine was attempted to elucidate more precisely the effect of addition of base and of acid to the reaction mixture of I and arylamine.

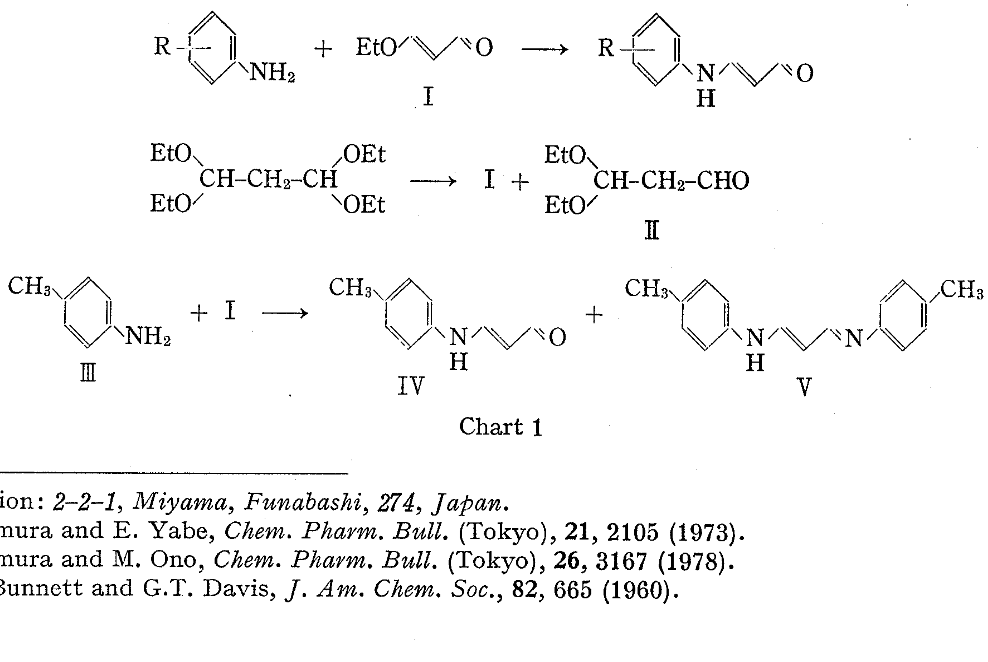

Chart 1

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[1] Location: *2-2-1, Miyama, Funabashi, 274, Japan.*

[2] S. Tamura and E. Yabe, *Chem. Pharm. Bull.* (Tokyo), **21**, 2105 (1973).

[3] S. Tamura and M. Ono, *Chem. Pharm. Bull.* (Tokyo), **26**, 3167 (1978).

[4] J.F. Bunnett and G.T. Davis, *J. Am. Chem. Soc.*, **82**, 665 (1960).

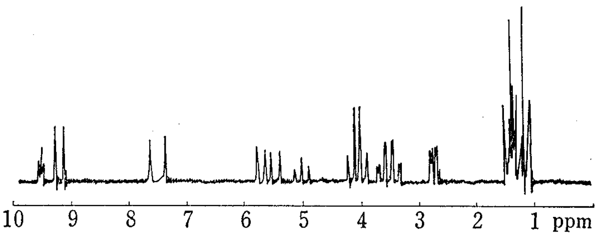

Fig. 1. NMR Spectrum of the Mixture of I and II (neat)

Unfortunately, I prepared from malonaldehyde bis (diethyl acetal)[2] includes malonaldehyde diethyl acetal (II) which could not be eliminated by fractional distillation. Nuclear magnetic resonance (NMR) spectrum of the mixture of I and II (Fig. 1) showed signals of I at δ 5.52 (double doublet, J=8 and 13 Hz, α-position), δ 7.52 (doublet, J=13 Hz, β-position) and δ 9.27 (doublet, J=8 Hz, aldehyde), and signals of II at δ 2.62 (double doublet, J=2 and 5 Hz, α-position), δ 4.97 (triplet, J=5 Hz, β-position) and δ 9.60 (triplet, J=2 Hz, aldehyde). Relative integrated intensities of these signals showed molar ratio of I and II in the mixture, and the ratio varied in an unexpected manner in repeated experiments under same condition, *i.e.*, the ratio of II to I varied from neary zero to one half.

The attempts were unsuccessful to eliminate II from the mixture by partial oxidation with silver oxide or by extraction with sodium hydrogen sulfite solution. After these treatments the ratio of II to I decreased, but did not reach to zero.

The preparation of pure I was carried out by heating the mixture of I and II in the presence of a trace of *p*-toluenesulfonic acid, followed by distillation under reduced pressure. In the NMR spectrum of I thus purified all the signals of II disappeared. Probably *p*-toluenesulfonic acid acts as a catalyst for dealcoholation of II to form I. Using I thus purified, the yield of preparation of β-arylaminoacrolein increased, *e. g.*, β-(*p*-chloroanilino)-acrolein was obtained in neary quantitative yield from I and *p*-chloroaniline, whereas a remarkable amount of malonaldehyde dianil was formed as the by-product in the reaction of *p*-chloroaniline and unpurified I.[2]

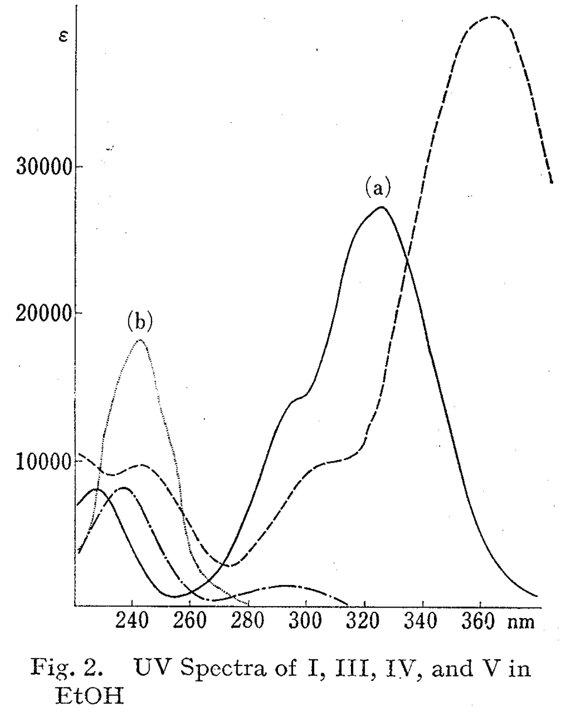

Fig. 2. UV Spectra of I, III, IV, and V in EtOH

(a)
IV: ———, III: —·—·—,
(b)
V: - - - -, I: ·········.

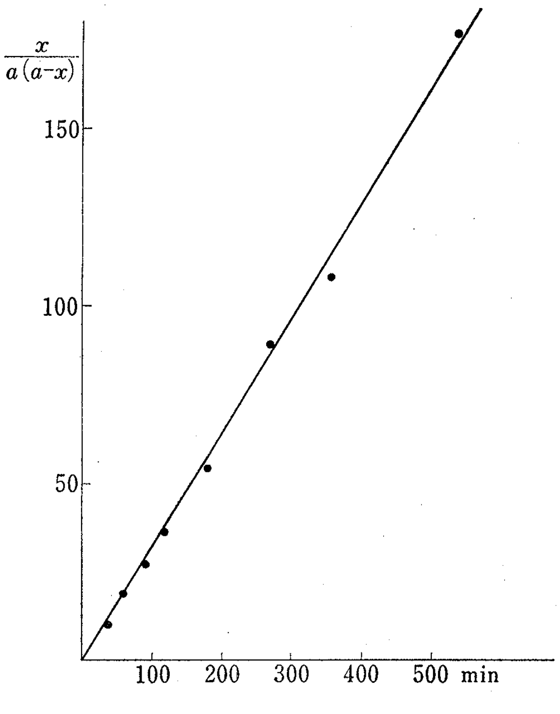

Fig. 3. Plot of $x/a(a-x)$ against Time for the Run with Equal Initial Concentration of I and III (Experimental Number 1, Table I)

a: initial concentration of I and III; x: concentration of IV at each measurement.

The ultraviolet absorption (UV) spectra of β-(*p*-toluidino)-acrolein (IV), 1-(*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (malonaldehyde dianil of *p*-toluidine) (V), *p*-toluidine (III) and I in ethanol are shown in Fig. 2.

In the kinetic study of the formation of IV in ethanol at 30°, optical densities of the reaction mixture were measured at 323, 325, 327, 371, 373 and 375 nm. If neccessary, aliquot part of the reaction mixture was diluted with ethanol before measurement. The concentrations of IV and V were calculated by the least square method neglecting the absorption by I and III in the case of equal initial concentration of I and III (experimental number 1, Table I). In each measurement, optical densities of the reaction mixture at 237, 243, 273, 285, 295 and 300 nm showed a good agreement with the values calculated from the results of the least square method using the extinction coefficients of each compound at given wave length. Formation of V was not more than 3% even when formation of IV reached 75%. A linear line was obtained by plotting $x/a(a-x)$ against time where a is the initial concentration of I and III, and x is the concentration of IV in each measurement (Fig. 3).

TABLE I. Formation of IV from I and III in EtOH at 30°

Experimental number	Initial concentrations (M)		Concentrations (M)		Pseudo first order rate constants k_1' (sec^{-1})	Second order rate constants k_2 (sec^{-1} mol^{-1})
	I	III	Et_3N	AcOH		
1	2×10^{-2}	2×10^{-2}				5.30×10^{-3}
2	2×10^{-2}	5×10^{-4}			1.12×10^{-5}	5.60×10^{-3}
3	2×10^{-2}	1×10^{-3}			1.10×10^{-5}	5.50×10^{-3}
4	2×10^{-2}	5×10^{-4}	2×10^{-2}		1.09×10^{-5}	5.45×10^{-3}
5	2×10^{-2}	5×10^{-4}		2×10^{-4}	1.21×10^{-5}	6.05×10^{-3}

Consequently, the reaction is second order. For examination of the effect of addition of triethylamine and of acetic acid, kinetic runs were carried out at lower initial concentration of III in the presence of excess I. Since in this case the absorption by I cannot be neglected, absorbance of I was subtracted from the optical densities at 323, 325 and 327 nm in each measurement. Good pseudo first order rate constants k'_1 were obtained and the results are shown in Table I. In the runs of experimental number 2, 3 and 4 (Table I) formation of V was negligible, while 2.7% formation of V was observed when formation of IV reached 88.3% in the presence of acetic acid (2×10^{-4} M, experimental number 5, Table I). As pointed out previously,[2] presence of acidic substance promotes the formation of malonaldehyde dianil in the reaction of I and arylamines. In the presence of 5×10^{-4} M acetic acid, 13.7% formation of V was observed when the formation of IV was calculated to be 65.4% by the above mentioned least square method (at 300 min after initiation of the reaction, initial concentrations of I and III being equal to those in experimental number 5). Clearly acetic acid accelerates the formation of V. When III (5×10^{-4} M) and IV (5×10^{-4} M) were reacted in ethanol in the presence of 5×10^{-4} M acetic acid at 30°, however, the formation of V was not more than 1% 300 min after initiation of the reaction.

The kinetic study of the formation of V from III and IV in ethanol was carried out at 30° in the presence of acetic acid in higher concentration of III. The results are shown in Table II.[5] The second order rate constant of the formation of V from III and IV is 7.55×10^{-3} sec^{-1} mol^{-1} in the presence of 8×10^{-3} M acetic acid. This means that the formation of V is expected to be 6.4% at 300 min with the initial concentration of 5×10^{-4} M of III and IV even in the presence of such a high concentration of acetic acid. Consequently, the

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[5] Formation of V from III and IV in the presence of acetic acid was comfirmed by the preparative experiment.

Table II. Formation of V from III and IV in EtOH at 30°

Initial concentrations (M) III	Initial concentrations (M) IV	Concentrations of AcOH (M)	Pseudo first order rate constants k_1' (sec^{-1})	second order rate constants k_2 (sec^{-1} mol^{-1})
4×10^{-3}	1×10^{-4}	4×10^{-3}	1.76×10^{-5}	4.40×10^{-3}
4×10^{-3}	1×10^{-4}	8×10^{-3}	3.55×10^{-5}	8.87×10^{-3}
4×10^{-3}	4×10^{-3}	8×10^{-3}		7.55×10^{-3}

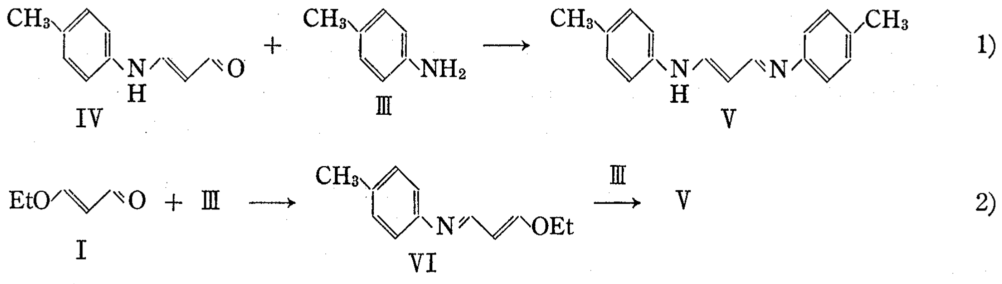

Chart 2

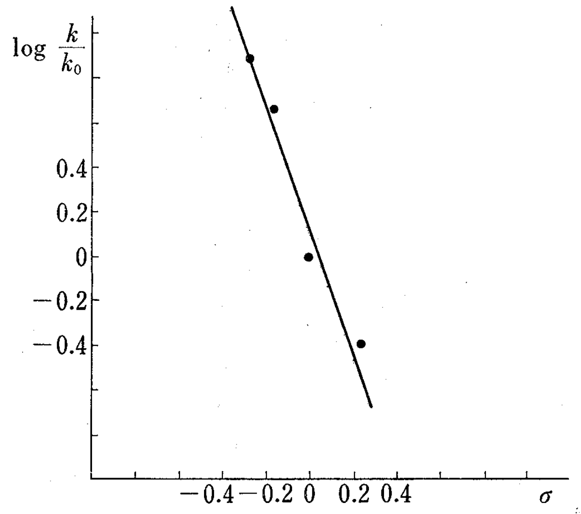

Fig. 4. Hammett Plot for Second Order Rate Constants k_2 of the Formation of β-Arylaminoacrolein Derivatives

formation of the major part of V in the reaction of I and III proceeds not *via* the reaction between III and IV (equation 1, Chart 2), but possibly the reaction expressed by the equation 2 in Chart 2. Since 1-ethoxy-3-(*p*-methylphenylimino)-1-propene (VI), an intermediate of this route, is yet unknown, further examination of this phenomenon could not be pursued.

In order to elucidate the substituent effect of the aromatic ring, kinetic study of the formation of β-arylaminoacroleins was carried out on the reaction of I and *p*-substituted arylamines in ethanol at 30°, and the following second order rate constants k_2 were obtained: *p*-methoxy, 9.70×10^{-3}; *p*-methyl (reexamined in the series of experiments), 5.66×10^{-3}; H, 1.19×10^{-3} and *p*-chloro, 5.00×10^{-4}. Hammett plot for k_2 is given in Fig. 4 (correlation coefficient=−0.9967), and the second order rate constant k_2 for each amine is represented by the equation $\log k_2 = -2.63\,\sigma - 2.74$.

Biggs and Robinson[6] introduced σ value of 1.239 for *p*-nitro substituent concerning the dissociation of conjugate acid of amine. Using Biggs's σ value, the second order rate constant of the formation of β-(*p*-nitroanilino)-acrolein is calculated to be 9.91×10^{-7} sec^{-1} mol^{-1}. This means that 80% formation of the product requires a reaction time of 47 days at 30° when I and *p*-nitroaniline are reacted in ethanol, each in the initial concentration of 1 M.

From the study on the exchange isotopic carbonyl oxygen with medium, Bender[7] proposed that hydrolysis reaction of ester proceeds through a tetrahedral intermediate. His

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6) A.I. Biggs and R.A. Robinson, *J. Chem. Soc.*, **1961**, 388.
7) M.L. Bender, *J. Am. Chem. Soc.*, 73, 1626 (1951).

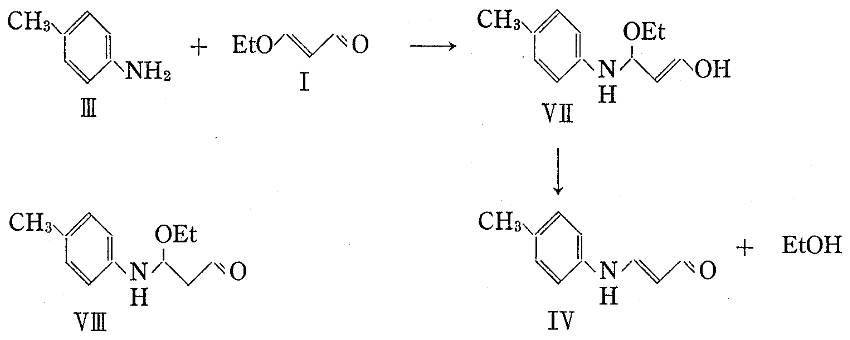

Chart 3

proposal have been supported by many investigators participating the kinetic study of carbonyl addition reaction in a broad sence. The present reaction proceeds through tetrahedral intermediate VII or VIII (Chart 3), and the possibility of the existence of VIII was ruled out by the observation that no deuterium atom is combined at the α-position of IV obtained from the reaction mixture of *p*-toluidine-N-d_2 and I in methanol-O-d.

Neither triethylamine nor acetic acid acts as an effective catalyst for the formation of IV from I and III (Table I). The reaction is probably catalyzed by the solvent, and for comparison, kinetic examination of the reaction of I and III in benzene, an aprotic solvent, was attempted.

The UV spectra of IV and V in benzene are shown in Fig. 5. The absorption maximum of both compounds showed bathochromic shift and a hypochromic change as compared with that observed in ethanol (Fig. 2). These differences are attributable to conformational isomerism of both compounds in each medium, *i. e.*, both compounds are in s-*trans* form in alcohol, while V is entirely in s-*cis* form in benzene and IV is mainly in s-*cis* form in benzene (Chart 4). In the NMR spectrum of IV in benzene-d_6 signals of α-position was observed at δ 4.94 (double doublet, J=2 and 8 Hz, s-*cis* form) and δ 5.76 (double doublet, J=8 and 13

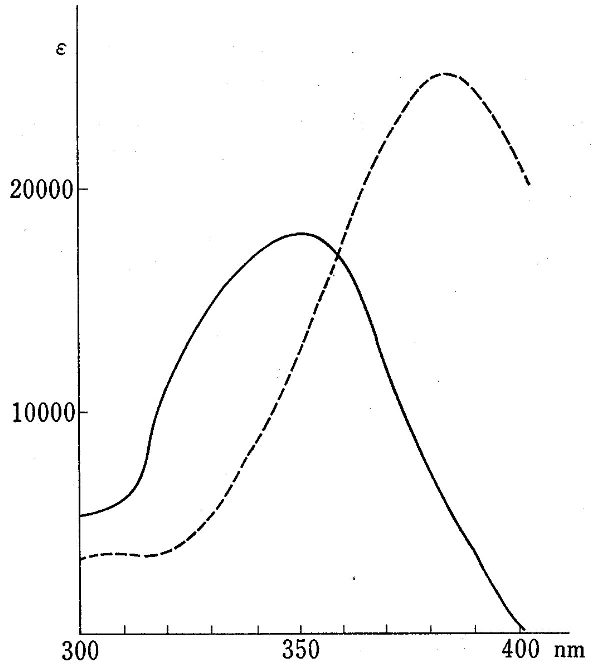

Fig. 5. UV Spectra of IV and V in Benzene

IV: ———, V: - - - -.

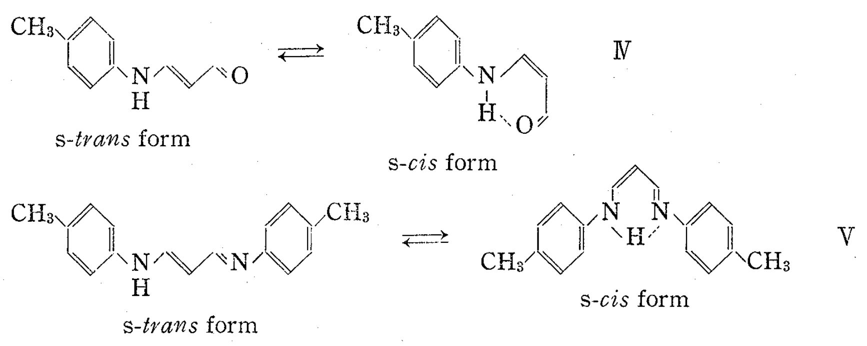

Chart 4

Hz, s-*trans* form). Relative integrated intensities of both signals indicate that IV consists of both s-*trans* and s-*cis* form (1:3) in benzene-d_6, while IV is entirely in s-*trans* form in deuteromethanol.[2] In the NMR spectrum of V in benzene-d_6 signals of s-*cis* form were observed at δ 4.90 (triplet, $J=6$ Hz, 2-position) and δ 7.47 (doublet, $J=6$ Hz, 1- and 3-position) and no signal of s-*trans* form was observed. In the NMR spectrum of V in deuteromethanol signals of s-*trans* form were observed at δ 5.85 (triplet, $J=11$ Hz, 2-position) and δ 7.91 (doublet, $J=11$ Hz, 1- and 3-position) and no signal of s-*cis* form was detected.

TABLE III. Formation of IV and V from I and III in Benzene at 30°

Reaction time (min)	Formation of IV (%)	Formation of V (%)
160	12.3	12.3
240	17.8	16.2
300	21.1	19.1
360	24.7	22.1
420	27.2	24.0
480	30.4	27.1

Calculated Value by Least Square Method.
Initial concentrations of I and III are 2×10^{-2} and 1 M, respectively.

The reaction of I and III in benzene at 30° was examined kinetically at 2×10^{-2} M initial concentration of I in the presence of excess III (1 M). The optical densities of the reaction mixture were measured at 349, 351, 353, 385, 387 and 389 nm and the concentrations of IV and V were calculated by the least square method. The results are shown in Table III. Formation of a remarkable amount of V was observed and the ratio of IV to V was neary constant in each measurement suggesting that V forms not through the route of equation 1 but the route of equation 2 (Chart 2). If an unknown intermediate such as VI exists in a significant amount, the result of the least square method will involve some error. At least it is clear that the formation of IV in the reaction of I and III is much slower in benzene than in ethanol, and that a remarkable amount of V forms in the reaction mixture. Further evidence for the formation of V was obtained by NMR measurement, *i. e.*, the signals of V as well as of IV were detected in the NMR spectrum of the reaction mixture of I and III in benzene-d_6. Consequently, benzene is not suitable solvent for the preparation of β-arylaminoacrolein derivatives from I and arylamines.

Experimental

All melting points are uncorrected. The UV spectra were measured on Hitachi spectrophotometer model 139 and the NMR spectra were recorded on JNM-PMX 60 NMR spectrometer using tetramethylsilane as internal standard.

Materials——β-Arylaminoacrolein derivatives used for measurement of UV spectra were prepared according to the previous paper.[2]

Preparation of I——A mixture of 133 g freshly distilled malonaldehyde bis (diethyl acetal)[2] and 13 g of 3% aqueous *p*-toluenesulfonic acid solution was heated on a boiling water bath for 20 min with stirring. The mixture was cooled by a mixture of ice and water, 1.3 g of $NaHCO_3$ was added and stirred for 5 min. The mixture was filtered and the filtrate was distilled under reduced pressure. The distillate was redistilled through a fractionating column 25 cm long under reduced pressure. The fraction boiling at 74—81°/21 mmHg was collected. Yield of the mixture of I and II was 30.0 g. To the mixture was added a trace of *p*-toluenesulfonic acid, the mixture was heated on an oil bath at 80° for 7 min under reduced pressure and then distilled under reduced pressure. The distillate was dissolved with ether, washed with aqueous $NaHCO_3$ solution and dried over K_2CO_3. After evaporation of the solvent, the residue was distilled under reduced pressure to give pure I boiling at 76—78°/17 mmHg. Yield was 16.8 g. In the NMR spectrum of I thus purified was detected no signals of II and malonaldehyde bis (diethyl acetal).

Preparation of V from III and IV——A mixture of 0.81 g of IV, 0.51 g of III and 0.30 g of AcOH in 10 ml EtOH was allowed to stand overnight at room temperature. The mixture was evaporated under reduced pressure and to the residue was added 200 ml of benzene and 20 ml of 7% aqueous $NaHCO_3$. The mixture was stirred for 5 hr to give a clear solution. Benzene layer was separated, dried over K_2CO_3 and evaporated. The residue was recrystallized from benzene to give 0.76 g of V, mp 163.5°, which was identified with authentic sample[2] by the comparison of their IR spectra and mixed melting point measurement.

Reaction of *p*-Toluidine-N-*d*$_2$ and I——To 0.54 g of *p*-toluidine was added 0.32 g of CH_3OD and resulted clear solution was evaporated under reduced pressure. This treatment was repeated 6 times and the residue was dissolved in 3 ml of CH_3OD. To the solution was added a solution of 0.50 g of I in 5 ml CH_3OD. The reaction mixture was allowed to stand overnight at room temperature and evaporated under reduced pressure. The residue was collected and recrystallized from benzene to give 0.45 g of IV, mp 122—123°. The NMR spectrum ($CDCl_3$) of IV thus obtained showed two double doublet signals of α-position at δ 5.28 (s-*cis* form) and δ 5.70 (s-*trans* form).[2] Relative integrated intensities of these signals indicates that one equivalent hydrogen atom is combined to α-position of the compound.