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Hydrolysis of Acyl Derivatives of Malonaldehyde Dianil. II.[1] Aminolysis and Alcoholysis of Acyl Derivatives of Malonaldehyde Dianil and β-Arylaminoacrolein

Machiko Ono and Shinzo Tamura*

School of Pharmaceutical Science, Toho University, 2-2-1, Miyama, Funabashi, 274, Japan

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Aminolysis and alcoholysis reactions of β-arylaminoacrolein and its *N*-acyl derivatives were studied. Acid-catalyzed aminolysis of β-(*N*-benzoyl-*p*-toluidino)acrolein (III) occurred at the β-position of III, accompaying the reversible interaction of the amine and the formyl group of III. In the reaction of III and amine in methanol under neutral conditions, aminolysis at the β-position of III and alcoholysis of the amide carbonyl group of III proceeded in parallel; the latter reaction was catalyzed by amine. In either case, no evidence for aminolysis at the amide carbonyl group of III was obtained. The reaction of the formyl group of III proceeded mainly when III and amine were reacted in benzene solution. Thus, 1-(*N*-benzoyl-*p*-methylphenylamino)-3-(*p*-chlorophenylimino)-1-propene (XII) was obtained when III and *p*-chloroaniline were reacted in benzene.

Alkaline hydrolysis of XII afforded 1-(*p*-methylphenylamino)-3-(*p*-chlorophenylimino)-1-propene (XIII), an unsymmetrical malonaldehyde dianil.

Aminolysis and alcoholysis reactions of 1-arylamino-3-arylimino-1-propene (malonaldehyde dianil) and its *N*-acyl derivatives were also studied. Alcoholysis occurred at the amide carbonyl group of *N*-acyl derivatives, while aminolysis occurred at the 1-position except for the case of 1-(*N*-phenylcarbamoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (XIV).

Keywords——aminolysis; alcoholysis; β-(*N*-benzoyl-*p*-toluidino)acrolein; β-(*N*-phenylcarbamoyl-*p*-toluidino)acrolein; 1-(*N*-benzoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene; 1-(*N*-benzoyl-*p*-methylphenylamino)-3-(*p*-chlorophenylimino)-1-propene; 1-(*p*-methylphenylamino)-3-(*p*-chlorophenylimino)-1-propene; 1-(*N*-phenylcarbamoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene

In the previous paper[1] we reported the hydrolysis reaction of 1-(*N*-benzoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (I); on heating at 60°C for 4 h in 80% aqueous dioxane solution in the presence of equimolar amounts of acetic acid and soldium acetate, I was hydrolyzed to form β-(*p*-toluidino)acrolein (II), *N*-benzoyl-*p*-toluidine and a small amount of β-(*N*-benzoyl-*p*-toluidino)acrolein (III). The reaction sequence was elucidated to be as shown in Chart 1.[2] In the reaction of β-(*N*-benzoylarylamino)acrolein (V) and arylamine, there are three possible courses (Chart 2). First, arylamine may attack the β-position of V to form *N*-benzoylarylamine and β-arylaminoacrolein (equation 1, Chart 2). Second, arylamine may attack the amide carbonyl carbon of V to form *N*-benzoylarylamine and β-arylaminoacrolein (equation 2, Chart 2). When the aryl moiety of the attacking amine is the same as that of V, both courses afford the same products. Third, arylamine may attack the formyl carbon of V to form the benzoyl derivative of malonaladehyde dianil (equation 3, Chart 2); this course corresponds to the reverse reaction of the first step of the hydrolysis of I (Chart 1).

N-Benzoyl-*p*-toluidine and β-(*N*-ethyl-*p*-toluidino)acrolein (VI) were obtained when III and *N*-ethyl-*p*-toluidine, which cannot react with III according to equation 3 (Chart 2), were reacted in 70% aqueous dioxane in the presence of equimolar amounts of acetic acid and sodium acetate. *N*-Benzoyl-*N*-ethyl-*p*-toluidine could not be detected in the reaction mixture. Compound VI was identical with an authentic sample prepared from *N*-ethyl-*p*-toluidine and malonaldehyde bis(dimethyl acetal). The reaction of III and *p*-chloroaniline was followed

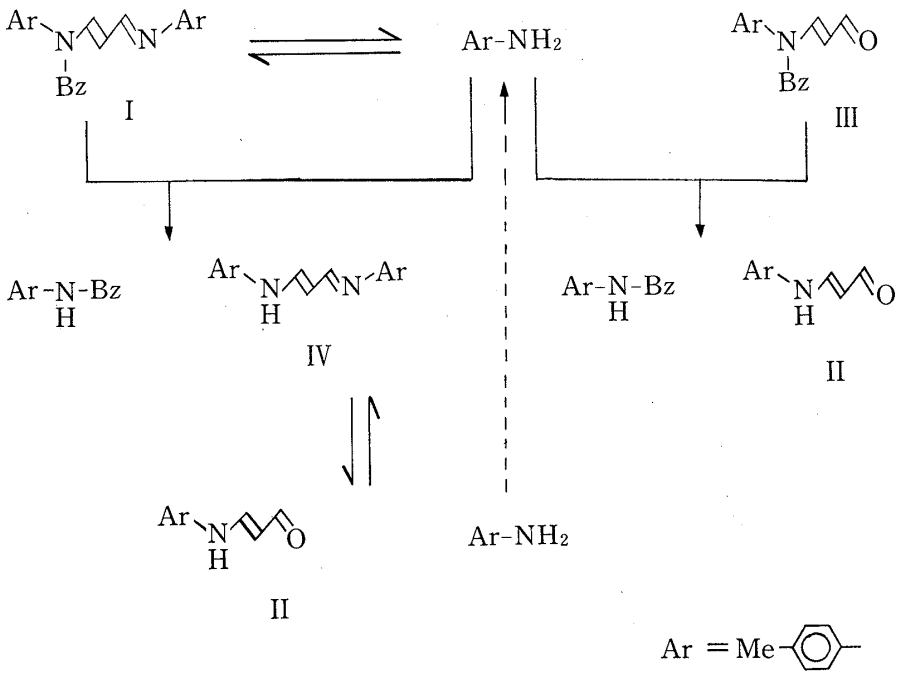


Chart 1

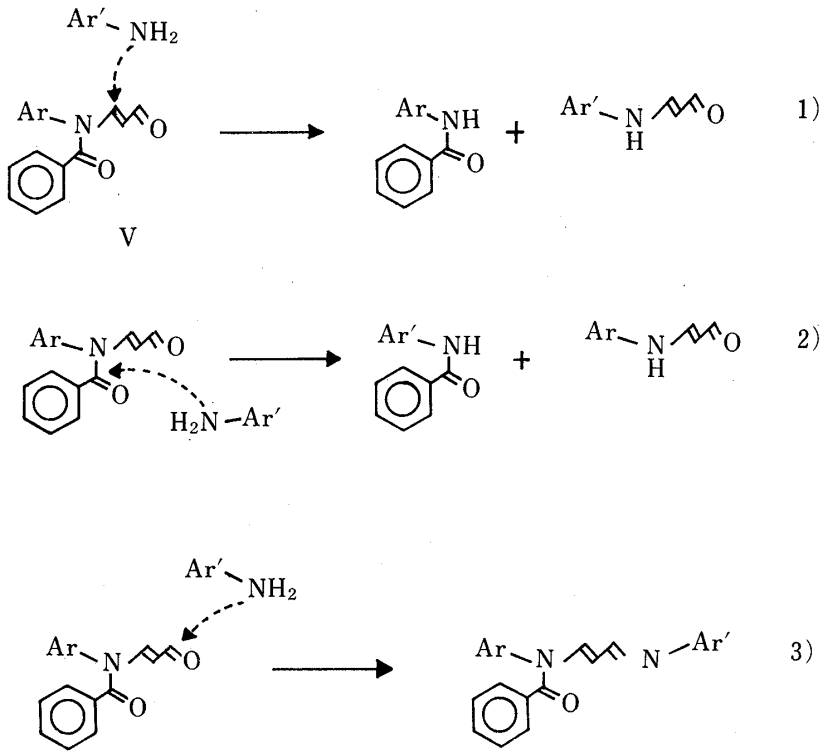


Chart 2

by ^{1}H nuclear magnetic resonance (^{1}H-NMR) spectroscopy of the reaction solution in deuterium oxide–dioxane-d_8 in the presence of acetic acid-d_4 and potassium deuteroacetate. The ^{1}H-NMR spectrum showed signals at δ 2.13 (methyl, singlet), 5.10 (α-position, double doublet, J=8, 14 Hz), 8.50 (β-position, doublet, J=14 Hz) and 9.43 (aldehyde, doublet, J=8 Hz) immediately after dissolution. After 160 min, weak signals were observed in addition to the above signals at δ 5.83 (triplet, J=10 Hz) and 7.88 (doublet, J=10 Hz). These signals may be attributable to 1-(*p*-chlorophenylamino)-3-(*p*-chlorophenylimino)-1-propene (malonaldehyde dianil of

p-chloroaniline) (VII). After one day, signals due to β-(*p*-chloroanilino)acrolein (VIII) were observed at δ 5.68 (α-position, double doublet, J=9, 13 Hz) and 9.17 (aldehyde, doublet, J=9 Hz) in addition to the above signals. After 7 days, the signals of III and VII disappeared, and a singlet signal due to the methyl group of *N*-benzoyl-*p*-toluidine was observed at δ 2.30. The final pattern was identical with that of a mixture of VIII and *N*-benzoyl-*p*-toluidine (Fig. 1).[3)]

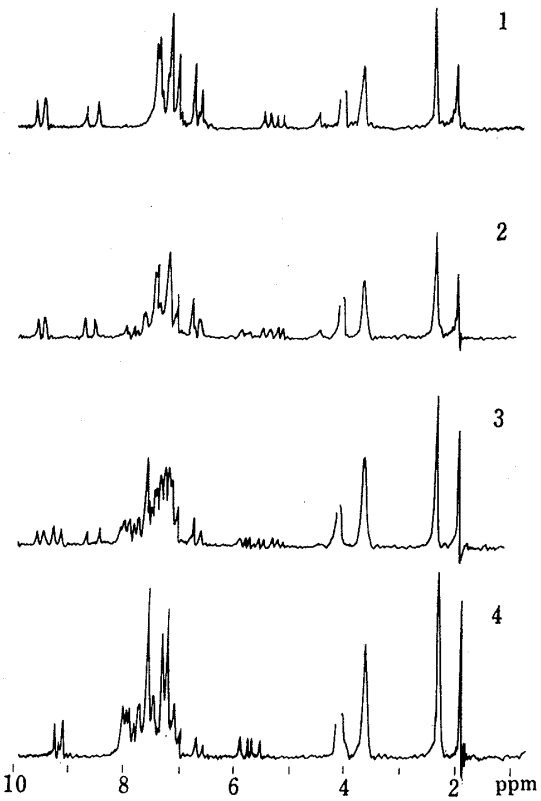


Fig. 1. Change of the ^{1}H-NMR Spectrum of the Reaction Solution of Equimolar Amounts of III and *p*-Chloroaniline in D_2O–Dioxane-d_8 in the Presence of CD_3COOD and CD_3COOK

1: immediately after dissolution.
2: at 160 min after dissolution.
3: at 24 h after dissolution.
4: at 7 d after dissolution.

The above results were confirmed by a preparative experiment, *i.e.*, VIII and *N*-benzoyl-*p*-toluidine were obtained by preparative thin layer chromatography (PTLC) from the reaction mixture in which III and *p*-chloroaniline had been reacted at 90°C for 225 min in 80% aqueous dioxane solution in the presence of equimolar amounts of acetic acid and sodium acetate, and neither II nor *N*-benzoyl-*p*-chloroaniline was detected in the reaction mixture. No evidence for the course corresponding to equation 2 could be obtained under the above reaction conditions. *N*-Benzoyl-*p*-toluidine and II were obtained when III and *p*-toluidine were reacted in methanolic solution at room temperature for one day, suggesting that the aminolysis reaction of III in methanol proceeds in the absence of any acidic substance. *N*-Benzoyl-*p*-toluidine, II, β-(*p*-anisidino)acrolein (IX) and 1-(*p*-methoxyphenylamino)-3-(*p*-methoxyphenylimino)-1-propene (malonaldehyde dianil of *p*-anisidine) (X) were obtained by PTLC from the reaction mixture in which III and *p*-anisidine had been reacted in methanolic solution at room temperature for one day. *N*-Benzoyl-*p*-anisidine could not be detected in the reaction mixture. The fact that II is produced but *N*-benzoyl-*p*-anisidine is not in the reaction of III and *p*-anisidine is inconsistent with the reaction scheme shown in Chart 2. From the first fraction of the above-mentioned PTLC, a small amount of a liquid substance was obtained; its ^{1}H-NMR spectrum was identical with that of methyl benzoate. The ^{1}H-NMR spectrum of a solution of III in methanol-d_4 showed no change on standing for one day. On the addition of a small amount of triethylamine to the solution, the signals of III disappeared and a multiplet signal due to the 2- and 6-positions of deuteromethyl benzoate was observed at δ 8.07, and the signal of the formyl group of II was observed at δ 9.16 as a mixture of doublet (J=9 Hz) and singlet signals at 90 min after the addition of triethylamine, suggesting that III was alcoholyzed to form II, and that a partial H–D exchange process occurred at the α-position of II in the presence of triethylamine. The ^{1}H-NMR spectrum of a methanol-d_4 solution of an equimolar mixture of IX and *p*-anisidine showed no change on standing for one day. In view of these observations, the reaction sequence of III and *p*-anisidine in methanol was presumed to be as shown in Chart 4. *N*-Benzoyl-*p*-toluidine, IX and X were obtained from the reaction mixture in which III and *p*-anisidine had been reacted in dioxane, and II could not be detected in the reaction mixture. *N*-Benzoyl-*p*-toluidine and VIII were obtained when III and *p*-chloroaniline were

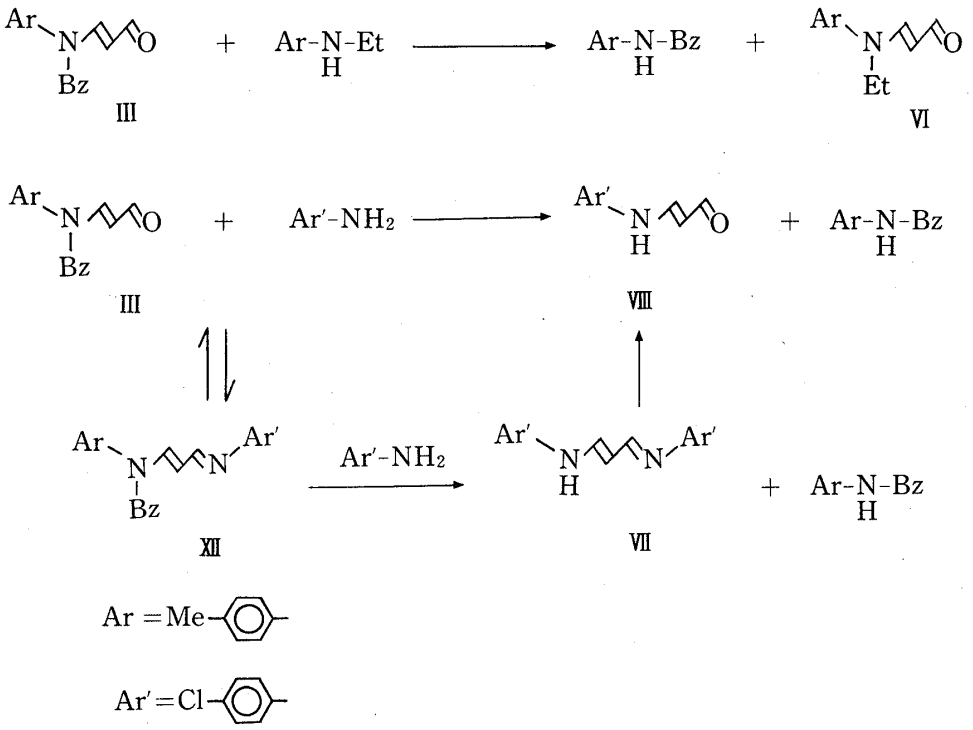


Chart 3

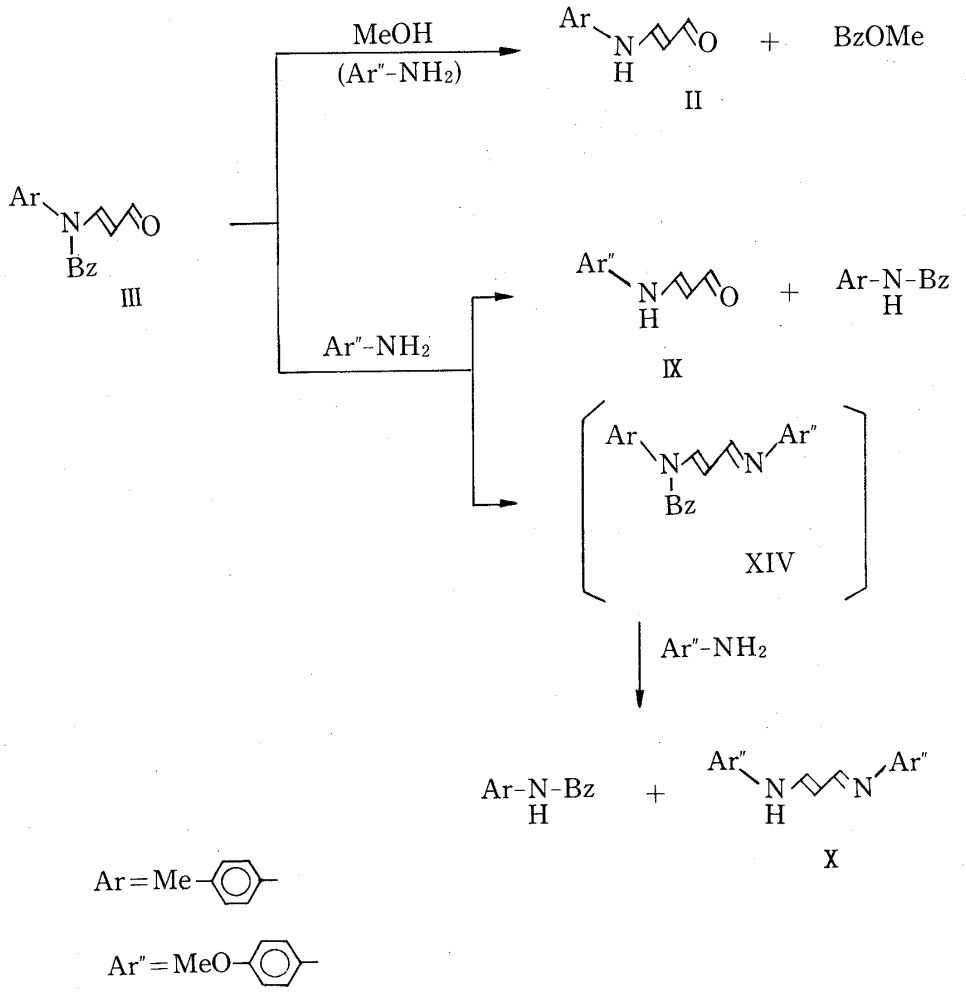


Chart 4

reacted in 80% aqueous dioxane at 57°C for 4 h, and II could not be detected in the reaction mixture. These observations support the presumption that II is formed by base-catalyzed methanolysis of III in the reaction of III and arylamine in methanolic solution. The reaction of III and aniline or *p*-chloroaniline was also followed by ^{1}H-NMR spectroscopy in methanol-d_4 solution. On standing of a methanol-d_4 solution of an equimolar mixture of III and aniline for one day, the signals of III disappeared and doublet signals (J=9 Hz) the formyl groups of II and β-anilinoacrolein (XI) were observed at δ 9.13 and 9.17, respectively, in the ^{1}H-NMR spectrum. The ratio of these signals was nearly unity, suggesting that the aminolysis and alcoholysis reactions of III proceed to similar extents. The reaction of III and *p*-chloroaniline, a weak base, was much slower than that of III and aniline or *p*-anisidine. The ^{1}H-NMR spectrum of a methanol-d_4 solution of an equimolar mixture of III and *p*-chloroaniline showed almost no change on standing for a day. After 11 days, the signals of III disappeared and doublet signals of the formyl groups of VIII and II were observed at δ 9.20 (J=9.5 Hz) and 9.13 (J=9 Hz), respectively. The former was smaller than the latter, suggesting that alcoholysis predominates over aminolysis in this case.

β-Arylaminoacrolein itself undergoes aminolysis by arylamine in methanolic solution. The ^{1}H-NMR spectrum of a methanol-d_4 solution of an equimolar mixture of XI and *p*-toluidine showed a singlet signal due to the methyl group of II at δ 2.28 besides the signal of the methyl group of *p*-toluidine (δ: 2.20). After 3 days, these two signals showed nearly equal intensities. From the above observations it was concluded that in the aminolysis reaction of III in polar solvents the course corresponding to equation 1 predominates under neutral conditions, and the courses corresponding to equations 1 and 3 proceed in parallel under acidic conditions. No evidence for the course corresponding to equation 2 was obtained. The alcoholysis reaction of III occurs at its amide linkage.

In contrast, the course corresponding to equation 3 predominates in the reaction of III and arylamine in nonpolar solvents. 1-(*N*-benzoyl-*p*-methylphenylamino)-3-(*p*-chlorophenylimino)-1-propene (XII) was obtained as colorless crystals melting at 200°C when III and *p*-chloroaniline were heated at 80°C for 13 h in benzene solution. Small amounts of VII and *N*-benzoyl-*p*-toluidine were formed as by-products. Alkaline hydrolysis of XII gave 1-(*p*-methylphenylamino)-3-(*p*-chlorophenylimino)-1-propene (XIII) as yellow crystals melting at 173°C. An equimolar mixture of 1-(*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (malonaldehyde dianil of *p*-toluidine) (IV) (mp 164°C) and VII (mp 158°C) melted at 172°C. The compound XIII can not be distinguished, therefore, from a mixture of IV and VII by elemental analysis or melting point measurement. The mass spectrum (MS) of XIII showed peaks at m/z 270 (M^+), 269, 164, 144, 111 and 91. MS of IV showed peaks at m/z 250 (M^+), 249, 144 and 91, and that of VII showed peaks at m/z 290 (M^+), 289, 164 and 111. The ^{1}H-NMR spectrum of XIII (deuterochloroform) showed multiplet signals of the 1- and 3-positions at δ 7.5—8; this pattern is clearly different from that of an equimolar mixture of IV and VII (Fig. 2).

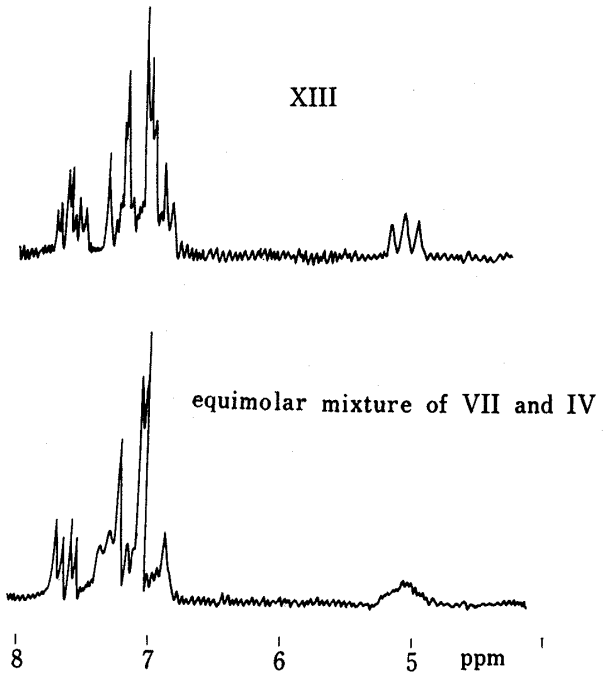
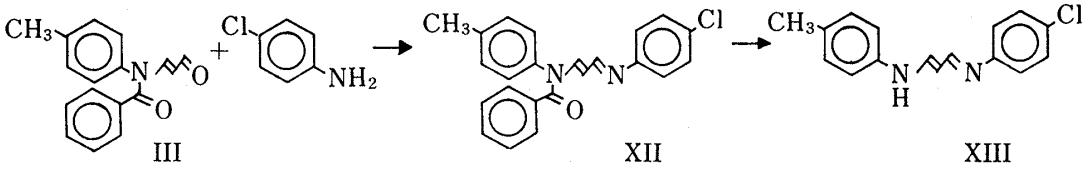


Fig. 2. ^{1}H-NMR Spectra ($CDCl_3$) of XIII and an Equimolar Mixture of VII and IV

N-Benzoyl-*p*-toluidine and X were obtained by PTLC from the reaction mixture in which equimolar amounts of III and *p*-anisidine had been reacted in benzene at room temperature for 3 days. 1-(*N*-Benzoyl-*p*-methylphenylamino)-3-(*p*-methoxyphenylimino)-1-propene (XIV) could not be detected in the reaction mixture. Presumably the reaction of XIV and *p*-anisidine, a stronger base than *p*-chloroaniline, proceeds more readily (to form X and *N*-benzoyl-*p*-toluidine) than the reaction of XII and *p*-chloroaniline. For the preparation of unsymmetrical malonaldehyde dianils, therefore, reaction between weakly basic amines and the benzoyl derivative of β-arylaminoacroleins derived from more strongly basic amines may be profitable.



III XII XIII

Chart 5

N-Benzoyl-*p*-toluidine and VII were obtained when equimolar amounts of III and *p*-chloroaniline were reacted at room temperature for one day in benzene in the presence of a small amount of acetic acid. The reaction was followed by ^{1}H-NMR spectroscopy of the benzene-d_6 solution in the presence of acetic acid-d_4. At 125 min after dissolution, a weak double doublet signal (J=9, 14 Hz) was observed at δ 5.87. The value of the chemical shift and the coupling pattern of the signal are identical with those of the 2-position of XII. No evidence for the existence of VIII in the solution could be obtained because the signals of VIII in the same solvent overlapped with the signals of the reactants. The reaction sequence remains unclear. However, it is clear that acids accelerate aminolysis at the β-position of III (equation 1, Chart 2) or at the 1-position of 1-(*N*-benzoylarylamino)-3-arylimino-1-propene. Compound XIII was also obtained when equimolar amounts of II and *p*-chloroaniline were reacted in benzene in the presence of acetic acid, but the purity of the product was rather unsatisfactory, *i.e.*, MS of the product showed small peaks at *m/z* 250 and 290 besides those of XIII. This means that IV and VII were contained in the product as impurities. The ^{1}H-NMR spectrum of an equimolar mixture of IV and *p*-anisidine in deuterochloroform changed on standing so that two singlet signals appeared at δ 2.22 and 3.82 besides signals at δ 2.30 (methyl of IV) and 3.77 (methoxy of *p*-anisidine), suggesting that exchange of the amine moiety occurs under these conditions. The ^{1}H-NMR spectrum of an equimolar mixture of IV and *p*-chloroaniline in deuterochloroform showed a similar change. Presumably amine exchange proceeds during the above-mentioned formation of XIII from from II and *p*-chloroaniline.

Aminolysis of I by *p*-chloroaniline occurs mainly at the 1-position in polar solvents. Thus XIII was obtained when I and *p*-chloroaniline were reacted in a mixture of methanol and dichloromethane. The purity of the product was unsatisfactory. The reaction of I and *p*-chloroaniline in dioxane solution gave similar results.

1-(*N*-Phenylcarbamoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (XVI) was formed when IV and phenyl isocyanate were reacted in dichloromethane at room temperature.

Compound XVI is heat-unstable; purification by the usual recrystallization technic was impossible, and it was purified by reprecipitation from its dichloromethane solution by addition of petroleum ether. When equimolar amounts of XVI and *p*-chloroaniline were reacted in benzene at room temperature for 2 days, *N*-phenyl-*N'*-(*p*-chlorophenyl)urea was precipitated from the solution, and IV was obtained from the mother liquor. When a mixture of XVI and ethanol was allowed to stand for 2 days, IV was precipitated from the solution, and ethyl phenylcarbamate and a small amount of *N*-phenyl-*N'*-(*p*-methylphenyl)urea were

obtained from the mother liquor. The aminolysis and alcoholysis of XVI occurred at its carbamoyl group. It is well known that urea readily undergoes aminolysis, and substituted ureas are prepared by this method.[4]

β-(*N*-Phenylcarbamoyl-*p*-toluidino)acrolein (XV) was obtained when II and phenyl isocyanate were reacted in dichloromethane at 40°C for 24 h. The ^{1}H-NMR spectrum of XV in methanol-d_4 showed no change on standing, suggesting that XV does not undergo alcoholysis under these conditions. Indeed, XV could be purified by recrystallization from ethanol.

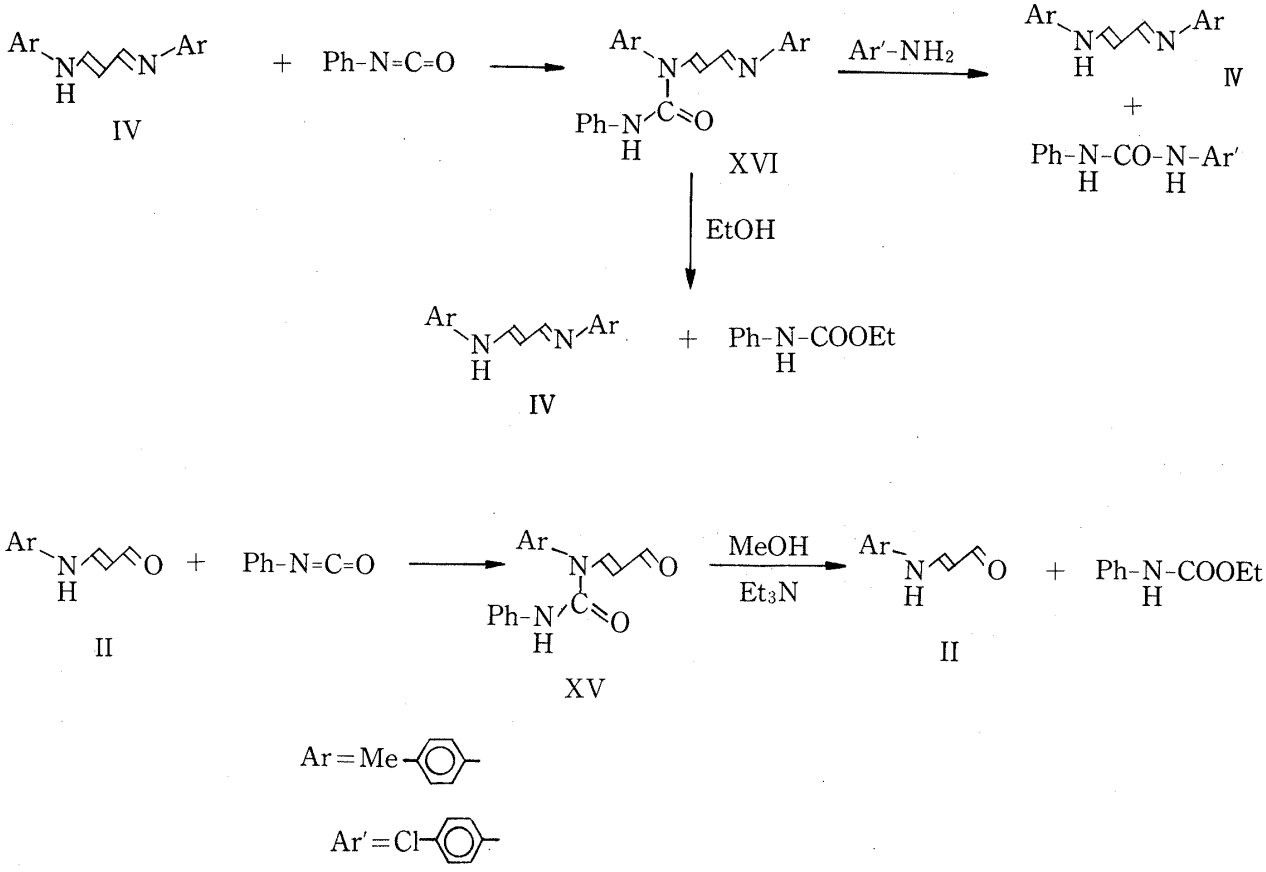


Chart 6

The base-catalyzed alcoholysis of III was described in the former part of this report. The same reactions of I and XV were also examined. The ^{1}H-NMR spectrum of XV in methanol-d_4 showed signals at δ 2.45 (methyl, singlet), 4.92 (α-position, double doublet, J=8, 14 Hz), 8.60 (β-position, doublet, J=14 Hz) and 9.35 (aldehyde, doublet, J=8 Hz). At 380 min after the addition of triethylamine to the solution, signals of II were observed at δ 2.28 (methyl, singlet), 5.63 (α-position, double doublet, J=9, 13 Hz), 7.93 (β-position, doublet, J=13 Hz) and 9.10 (aldehyde, doublet, J=9 Hz). After one day, signals of XV disappeared, and partial H–D exchange was observed at the α-position of II. Methyl benzoate and IV were obtained when I was reacted with sodium methoxide in a mixture of methanol and tetrahydrofuran at room temperature for a day. The alcoholysis of acyl derivatives of II or IV occurred at their amide carbonyl groups.

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), double doublet (dd), triplet (t) and quartet (q). PTLC was performed on silica gel with benzene–AcOEt (4: 1) as a developing solvent.

Compounds I and III were prepared according to the previous paper[1] and compounds II, IV, VII, VIII, IX and X were prepared according to earlier papers.[5]

The samples of II, IV, VII, VIII, IX, X and *N*-benzoyl-*p*-toluidine described in this experimental part were identical with authentic samples as judged by mixed melting point measurement and comparison of their IR spectra.

β-(*N*-Ethyl-*p*-toluidino)acrolein (VI)——A solution of *N*-ethyl-*p*-toluidine (10 g), malonaldehyde bis (dimethyl acetal) (18.2 g) and 36% HCl (7.7 ml) in 70 ml of EtOH was allowed to stand at room temperature for 24 h. The mixture was made alkaline by addition of 120 ml of 7% $NaHCO_3$ and concentrated under reduced pressure. The residue was extracted with ether, and the extract was concentrated under reduced pressure. The residue was made alkaline by addition of $NaHCO_3$ and steam-distilled. The residue was extracted with ether. The extract was dried over K_2CO_3, and concentrated under reduced pressure. Distillation of the residue under reduced pressure gave 4.05 g of VI. bp 120°C/0.05 mmHg. *Anal.* Calcd for $C_{12}H_{15}NO \cdot 1/4H_2O$: C, 74.39; H, 8.06; N, 7.23. Found: C, 74.12; H, 8.07; N, 7.12. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, CH_3 of Et, t, $J=7$ Hz), 2.35 (3H, CH_3, s), 3.73 (2H, CH_2 of Et, q, $J=7$ Hz), 5.40 (1H, α-position, dd, $J=8$, 13 Hz), 7.42 (1H, β-position, d, $J=13$ Hz) and 9.27 (1H, CHO, d, $J=8$ Hz).

1-(*N*-Phenylcarbamoyl-*p*-methylphenylamino)-3-(*p*-methylphenylimino)-1-propene (XVI)——A solution of 1.79 g of phenyl isocyanate in 10 ml of CH_2Cl_2 was added to a solution of 3.76 g of IV in 60 ml of CH_2Cl_2. The mixture was allowed to stand at room temperature for 30 min, then concentrated under reduced pressure. The residue was dissolved in a small amount of CH_2Cl_2, and 100 ml of petroleum ether was added to the solution. The precipitate was collected to give 4.85 g (83%) of crude XVI. Reprecipitation gave 3.51 g (63%) of pure XVI. mp 127°C. *Anal.* Calcd for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.27; N, 11.37. Found: C, 78.10; H, 6.33; N, 11.26. ^{1}H-NMR ($CDCl_3$) δ: 2.31 (3H, CH_3, s), 2.45 (3H, CH_3, s), 5.37 (1H, 2-position, dd, $J=9$, 14 Hz), 6.43 (1H, NH, s), 8.18 (1H, 3-position, d, $J=9$ Hz) and 8.28 (1H, 1-position, d, $J=14$ Hz).

β-(*N*-Phenylcarbamoyl-*p*-toluidino)acrolein (XV)——A solution of 2.98 g of phenyl isocyanate in 20 ml of CH_2Cl_2 was added to a solution of 1.61 g of II in 20 ml of CH_2Cl_2. The mixture was warmed at 40°C on a water bath for 24 h and concentrated under reduced pressure. The residue was allowed to stand in a refrigerator after addition of 15 ml of anhydrous ether. The precipitate was collected to give 2.19 g (78%) of crude XV. Recrystallization from EtOH gave 1.52 g (54%) of pure XV. mp 128.5°C. *Anal.* Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.73; H, 5.66; N, 9.90. ^{1}H-NMR ($CDCl_3$) δ: 2.47 (3H, CH_3, s), 5.03 (1H, α-position, dd, $J=8$, 14 Hz), 6.52 (1H, NH, s), 8.58 (1H, β-position, d, $J=14$ Hz) and 9.50 (1H, CHO, d, $J=8$ Hz).

Reaction of III and *N*-Ethyl-*p*-toluidine in Aqueous Dioxane in the Presence of AcOH and AcONa——A solution of 60 mg of AcOH and 136 mg of $AcONa \cdot 3H_2O$ in 5 ml of H_2O was added to a solution of 0.27 g of III and 0.135 g of *N*-ethyl-*p*-toluidine in 11 ml of dioxane. The mixture was heated at 60°C for 9.5 h on a water bath. The mixture was made alkaline by addition of 10 ml of 7% $NaHCO_3$ and concentrated under reduced pressure. The residue was extracted with benzene. The extract was dried over K_2CO_3, and concentrated. The residue was extracted with ether. From the residue, 69 mg of *N*-benzoyl-*p*-toluidine was obtained, and from the extract a small amount of III and 50 mg of VI were obtained by PTLC.

Reaction of III and *p*-Chloroaniline in Aqueous Dioxane in the Presence of AcOH and AcONa——A solution of 0.12 g of AcOH and 0.27 g of $AcONa \cdot 3H_2O$ in 5 ml of H_2O was added to a warm solution of 0.54 g of III in 10 ml of dioxane. A solution of 0.25 g of *p*-chloroaniline in 10 ml of dioxane was added. The mixture was heated at 90°C for 225 min on a water bath, made alkaline by addition of 5 ml of 10% Na_2CO_3, and concentrated under reduced pressure. The residue was extracted with 10 ml of benzene. The extract was dried over Na_2SO_4 and evaporated to dryness. The residue was dissolved in EtOH, and an EtONa solution made from 0.1 g of Na was added to the solution. EtOH was evaporated off under reduced pressure, and the residue was extracted with ether. From the residue, 30 mg of VIII was obtained by treatment with a small amount of 7% $NaHCO_3$, and from the extract, 100 mg of *N*-benzoyl-*p*-toluidine was obtained.

Reaction of III and *p*-Toluidine in MeOH——*p*-Toluidine (0.054 g) was added to a warm solution of 0.13 g of III in 2 ml of anhydrous MeOH and the solution was allowed to stand at room temperature for one day. The solution was concentrated under reduced pressure, and the residue was subjected to PTLC to give 35 mg of *N*-benzoyl-*p*-toluidine and 28 mg of II. A small amount of a liquid substance was obtained from the first fraction of PTLC. Its ^{1}H-NMR spectrum ($CDCl_3$) was identical with that of methyl benzoate.

Reaction of III and *p*-Anisidine in MeOH——*p*-Anisidine (0.25 g) was added to a warm solution of 0.53 g of III in 4 ml of anhydrous MeOH. The mixture was allowed to stand at room temperature for one day. The precipitate was collected and recrystallized from benzene to give 0.19 g of X. The mother liquor was concentrated under reduced pressure, and the residue was subjected to PTLC to give 0.20 g of *N*-benzoyl-*p*-toluidine, 30 mg of II and 15 mg of IX. A small amount of a liquid substance was obtained from the first fraction of PTLC. Its ^{1}H-NMR spectrum ($CDCl_3$) was identical with that of methyl benzoate.

Reaction of III and *p*-Anisidine in Dioxane——*p*-Anisidine (0.06 g) was added to a warm solution of 0.13 g of III in 0.8 ml of dioxane. The mixture was allowed to stand at room temperature for one day. The mixture was subjected to PTLC to give 45 mg of *N*-benzoyl-*p*-toluidine, 10 mg of X and 10 mg of IX.

Reaction of III and *p*-Chloroaniline in Benzene——A solution of 0.15 g of III and 0.07 g of *p*-chloroaniline in 6 ml of benzene was heated at 85°C for 13 h on a water bath. The solution was concentrated under reduced pressure, and the residue was extracted with ether. The residue (60 mg) was recrystallized from benzene to give 43 mg of XII. *Anal.* Calcd for $C_{23}H_{19}N_2OCl$: C, 73.69; H, 5.11; N, 7.47. Found: C, 73.58; H, 5.16; N, 7.37. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, CH_3, s), 5.70 (1H, 2-position, dd, J=9, 15 Hz), 8.15 (1H, 1-position, d, J=9 Hz) and 8.28 (1H, 3-position, d, J=15 Hz). The mother liquor was concentrated under reduced pressure. The residue was subjected to PTLC to give 15 mg of *N*-benzoyl-*p*-toluidine and 10 mg of VII.

Alkaline Hydrolysis of XII——A mixture of a solution of 0.11 g of XII in 7 ml of dioxane and 3 ml of 0.1 N NaOH was stirred at room temperature for 2 d. After the removal of undissolved XII (30 mg) by filtration, 7% $NaHCO_3$ was added to the filtrate, and the mixture was concentrated under reduced pressure to remove most of the dioxane. The residue was extracted with benzene. From the $NaHCO_3$ layer, 8 mg of benzoic acid was obtained. The benzene layer was dried over K_2CO_3 and concentrated under reduced pressure. The residue was recrystallized from benzene to give 10 mg of XIII. mp 173°C. *Anal.* Calcd for $C_{16}H_{15}ClN_2$: C, 70.98; H, 5.58; N, 10.35. Found: C, 69.99; H, 5.40; N, 9.92. ^{1}H-NMR ($CDCl_3$): 2.36 (3H, CH_3, s), 5.12 (1H, 2-position, t, J=6 Hz) and 7.71 (2H, 1- and 3-position, multiplet).

Reaction of III and *p*-Anisidine in Benzene——*p*-Anisidine (0.09 g) was added to a warm solution of 0.20 g of III in 2 ml of benzene. The mixture was allowed to stand at room temperature for 3 d. The precipitate was collected, and recrystallized from benzene to give 60 mg of X. The mother liquor was concentrated under reduced pressure and the residue was subjected to PTLC to give a small amount of III and 60 mg of *N*-benzoyl-*p*-toluidine.

Reaction of III and *p*-Chloroaniline in Benzene in the Presence of AcOH——A solution of 0.04 g of AcOH in 1 ml of anhydrous benzene was added to a solution of 0.27 g of III and 0.13 g of *p*-chloroaniline in 6 ml of anhydrous benzene. The mixture was allowed to stand at room temperature for a day. The precipitate was collected and added to 7% $NaHCO_3$. The mixture was extracted with benzene, and the extract was dried over K_2CO_3 and concentrated. The residue was recrystallized from benzene to give 0.10 g of VII. The mother liquor was washed with 7% $NaHCO_3$, dried over K_2CO_3 and concentrated. The residue was subjected to PTLC to give a small amount of III and 75 mg of *N*-benzoyl-*p*-toludine.

Reaction of I and *p*-Chloroaniline in a Mixture of CH_2Cl_2 and MeOH——A solution of 1.18 g of I and 0.43 g of *p*-chloroaniline in a mixture of 4 ml of anhydrous CH_2Cl_2 and 12 ml of MeOH was allowed to stand at room temperature for one day. The mixture was concentrated under reduced pressure and 3 ml of EtOH was added to the residue. The precipitate was collected and recrystallized from benzene to give 0.33 g of crude XIII. The mother liquor was concentrated under reduced pressure and 5 ml of ether was added to the residue. The precipitate was collected and recrystallized from benzene to give 0.30 g of *N*-benzoyl-*p*-toluidine. The mother liquor was evaporated to dryness, and the residue was subjected to PTLC to give 0.19 g of *N*-benzoyl-*p*-toluidine and a small amount of methyl benzoate, which was distilled under reduced pressure, and shown to be identical with an authentic sample by comparison of their IR spectra.

Reaction of XVI and *p*-Chloroaniline in Benzene——A solution of 0.64 g of *p*-chlotoaniline in 3 ml of benzene was added to a solution of 1.80 g of XVI in 75 ml of benzene. The mixture was allowed to stand at room temperature for 2 d. The precipitate was collected to give 0.53 g of crude *N*-phenyl-*N'*-(*p*-chlorophenyl)urea; MS showed a small peak at *m/z* 226, suggesting that *N*-phenyl-*N'*-(*p*-methylphenyl)urea was contained in the sample. Recrystallization of the crude *N*-phenyl-*N'*-(*p*-chlorophenyl)urea from benzene afforded 0.38 g of pure sample. mp 235°C. It was found to be identical with authentic sample by mixed melting point measurement and comparison of their IR spectra. The mother liquor was concentrated under reduced pressure. The residue was washed with 5 ml of EtOH and recrystallized from benzene to give 0.59 g of crude IV. MS of the sample showed small peaks at *m/z* 290 and 270 suggesting that small amounts of VII and XIII were contained in the sample.

Alcoholysis of XVI——Compound XVI (1.85 g) was added to 20 ml of anhydrous EtOH, and the mixture was allowed to stand at room temperature for 2 d. The precipitate was collected, and recrystallized from benzene to give 0.79 g of IV. The mother liquor was concentrated under reduced pressure. The residue was applied to a silica gel column, and eluted with benzene to give 0.07 g of *N*-phenyl-*N'*-(*p*-methylphenyl)-urea and 0.28 g of ethyl phenylcarbamate. mp 49°C. It was shown to be identical with an authentic sample by mixed melting point measurement and comparison of their IR spectra.

Reaction of I and MeONa——Compound I (1.18 g) was dissolved in 10 ml of tetrahydrofuran with warming to 60°C, then 30 ml of anhydrous MeOH was added to the solution. A solution of MeONa in MeOH (prepared from 0.075 g of Na and 5 ml of anhydrous MeOH) was added to the above solution. The mixture was allowed to stand at room temperature for one day, and 10 ml of 7% $NaHCO_3$ was added to the mixture. The mixture was concentrated under reduced pressure to remove most of the tetrahydrofuran. The residue was extracted with $CHCl_3$. From the water layer, 30 mg of benzoic acid was obtained. The $CHCl_3$ layer was washed with H_2O, dried over K_2CO_3 and concentrated under reduced pressure. EtOH was added to the residue, and the insoluble part was collected and recrystallized from benzene to give 0.73 g of IV. The mother liquor was concentrated under reduced pressure. The residue was applied to a alumina column, and eluted with benzene to give 20 mg of methyl benzoate which was distilled under reduced pressure, and shown

to be identical with an authentic sample by comparison of their IR spectra.

References and Notes

1) Part I: S. Tamura and M. Ono, *Chem. Pharm. Bull.*, **29**, 308 (1981).
2) This chart was also published in ref. 1.
3) As well as the processes mentioned, partial H-D exchange at the α-position of VIII was observed, as shown in Fig. 1.
4) T.L. Davis and K.C. Blanchard, "Organic Syntheses," Coll. Vol. I, ed. by H. Gilman, John Wiley and Sons, Inc., New York, 1932, p. 453; F. Kurzer, "Organic Syntheses," Coll. Vol. IV, ed. by N. Robjohn, John Wiley and Sons, Inc., New York, 1963, p. 52.
5) S. Tamura and E. Yabe, *Chem. Pharm. Bull.*, **21**, 2105 (1973); S. Tamura and E. Takeda, *Chem. Pharm. Bull.*, **27**, 403 (1979); S. Tamura, M. Ono, and K. Furuyama, *Chem. Pharm. Bull.*, **28**, 2356 (1980).