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Condensations of 1,4-Cyclohexanediones and Secondary Aromatic Amines. The Formation of Alkyldiarylamines and Triarylamines

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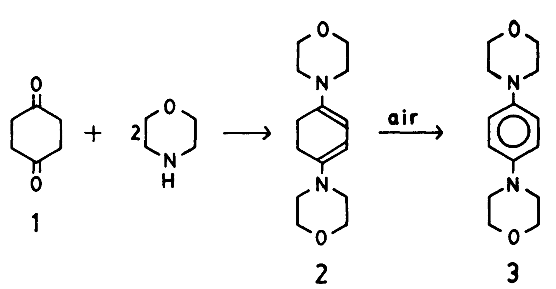
(Received September 26, 1983)

Condensation of 1,4-cyclohexanedione with *N*-alkylarylamines gives *N*-alkyl-*N*-arylanilines, and that with diarylamines gives triarylamines. A mechanism involving dehydration of monoenamines of the 1,4-dione is proposed for the reaction. Relative rates of substituted *N*-ethylanilines on competitive reactions plotted *vs.* Hammet's σ values gave -2.0 as the ρ value. In separate reactions, however, a different tendency is noted for the yield, that is, the ease of reactions with *p*-chloro and *p*-nitro derivatives. This discrepancy is explained in terms of acidities of the conjugate acids of the amines used as the actual catalysts.

The condensations between ketones and secondary amines are known to produce enamines. Leonard and Sauers[1] reported that the condensation of 1,4-cyclohexanedione (**1**) with cycloalkylamines gave dienediamines, which converted by air oxidation to substituted *p*-phenylenediamines.

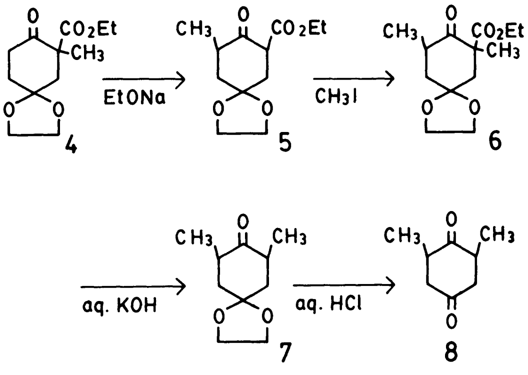


(1)

On the condensation of **1** with some secondary aromatic amines, we now have found that almost no dienediamines or phenylenediamines are obtained, but that tertiary monoamines are produced instead. In the present study, a mechanism for the reaction will be proposed and substituent effects will be discussed. This reaction is useful as a new procedure for the synthesis of tertiary aromatic amines. Preparation of 2,6-dimethyl-1,4-cyclohexanedione is also reported.

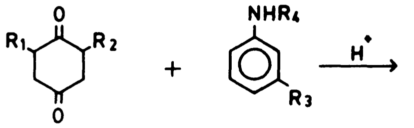
Results and Discussion

Preparation of 2,6-Dimethyl-1,4-cyclohexanedione. 2,6-Dimethyl-1,4-cyclohexanedione (**8**), one of the starting materials for the condensation reaction, was prepared as shown in Scheme 1. Ethyl 5,5-ethylenedioxy-3-methyl-2-oxocyclohexanecarboxylate (**5**) was obtained by isomerization of ethyl 5,5-ethylenedioxy-1-methyl-2-oxocyclohexanecarboxylate (**4**), and was methylated *in situ* in considerable yield. The alkaline hydrolysis of the product **6** yielded the monoacetal **7**, which on removal of the ethylenedioxy group gave 2,6-dimethyl-1,4-cyclohexanedione (**8**). This procedure was modified from the method of Mori and Matsui[2] for the methylation of ethyl 1-methyl-2-oxocyclohexanecarboxylate to afford ethyl 1,3-dimethyl-2-oxocyclohexanecarboxylate. This method for α,α'-dialkylation of cyclic ketones, exploiting the reversible cleavage of β-keto ester, was also useful for the formation of the 1,4-dione derivative.

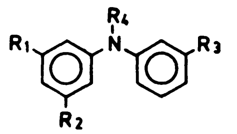


Scheme 1.

Condensation Reaction. When the condensation of **1** and *N*-methylaniline (**9**) was carried out in the presence of *p*-toluenesulfonic acid, *N*-methyl-*N*-phenylaniline (**10**) was obtained unexpectedly in 77% yield. The condensation of **1** with *N*-methyl-*m*-toluidine (**11**) in similar conditions gave *N*-methyl-*N*-phenyl-*m*-toluidine (**12**) which was produced also from 2-methyl-1,4-cyclohexanedione (**13**) on the reaction with *N*-methylaniline (**9**). Even diphenylamine (**14**) which is a very weak base (pK_a=0.79) reacted with **1** giving triphenylamine (**15**) in 72% yield, and with 2,6-dimethyl-1,4-cyclohexanedione (**8**) giving 3,5-dimethyltriphenylamine (**16**).



1: $R_1=R_2=H$ **9**: $R_3=H$, $R_4=CH_3$
13: $R_1=H$, $R_2=CH_3$ **11**: $R_3=R_4=CH_3$
8: $R_1=R_2=CH_3$ **14**: $R_3=H$, $R_4=C_6H_5$



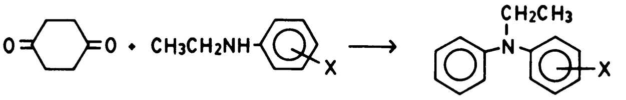
(2)

10: $R_1=R_2=R_3=H$, $R_4=CH_3$
12: $R_1=R_2=H$, $R_3=R_4=CH_3$
15: $R_1=R_2=R_3=H$, $R_4=C_6H_5$
16: $R_1=R_2=CH_3$, $R_3=H$, $R_4=C_6H_5$

These reactions (Eq. 2) show that the 1,4-diones are converted into aniline derivatives, not the product in Eq. 1, and that the amines combine selectively to the carbonyl having no substituent at α-position.

Thus, the effect of the substituent on the starting aniline was examined in order to obtain insight into

TABLE 1. CONDENSATIONS OF 1, 4-CYCLOHEXANEDIONE AND *N*-ETHYLANILINES



X	Reaction time/h	Product			
		Yield/%	Appearance	NMR(δ, CCl_4)	MS (rel intensity/%)
p-CH_3O	12	50.6	Cryst mp 58—59 °C	1.17(3H, t), *ca.* 3.66(2H, q), 3.77(3H, s), 6.50—7.40(9H, m)	227(75)M^+, 212(100)
p-CH_3	12	42.9	Light yellow liquid	1.18(3H, s), 2.29(3H, s), 3.69(2H, q), 6.45—7.25(9H, m)	211(100)M^+, 197(62), 196(70)
m-CH_3	12	38.4	Light yellow liquid	1.20(3H, t), 2.27(3H, s), 3.71(2H, q), 6.45—7.20(9H, m)	211(100)M^+, 196(81)
o-CH_3	12	23.9	Light yellow liquid	1.20(3H, t), 2.10(3H, s), 3.61(2H, q), 6.18—7.20(9H, m)	211(58)M^+ 196(100)
H	12	58.6	Colorless liquid	1.14(3H, t), 3.67(2H, q), 6.65—7.50(10H, m)	197(62)M^+, 182(100)
p-Cl	12 35	75.7 85.1	Colorless liquid	1.18(3H, t), 3.68(2H, q), 6.58—7.30(9H, m)	233(18), 231(56), 216(100)
p-NO_2	12 35	73.1 83.0	Red cryst mp 72—73 °C	1.25(3H, t), 3.80(2H, q), 6.35—6.70(2H, m), 6.75—7.68(5H, m), 7.80—8.13(2H, m)	242(59)M^+, 227(100)

the reaction mechanism. Table 1 shows the results of the condensation of **1** with some substituted *N*-ethylanilines. No definite relationship can be found between the yields of the tertiary amines and the basicity of the starting amines. However, it is worth noting that *p*-nitro and *p*-chloro substitutions lead to good yield. Therefore, **1** was treated in a solution containing *N*-ethylaniline and another aniline, and the products were analyzed by means of gas chromatography. The relative rates on the competing reactions plotted *vs.* Hammet's σ values gave -2.0 as the ρ value, as shown in Fig. 1. The reactivities, hence, decrease with the decrease of the basic strengths of the amines. In addition to Fig. 1, *N*-ethyl-*p*-nitroaniline was found to react very slowly in the competitive reaction with *N*-ethylaniline.

The aromatization of cyclohexane ring was also found on condensation of 4,4-(ethylenedioxy)cyclohexanone (**17**) with secondary aromatic amines. The reaction of **17** with *N*-methylaniline produced *N*-methyl-*N*-phenylaniline and the diacetal **18** of the 1,4-dione.

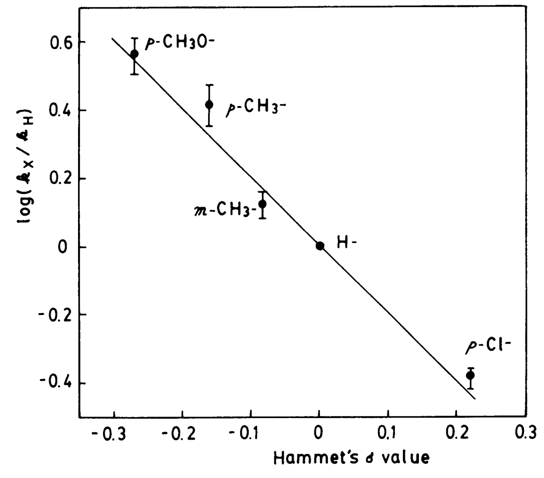
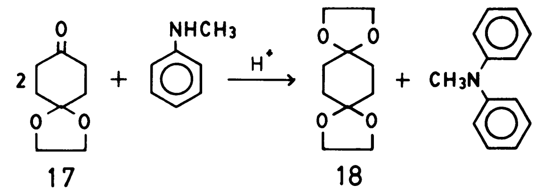
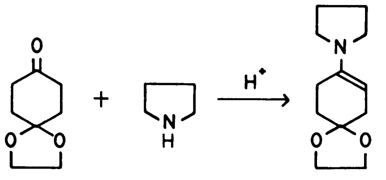


Fig. 1. Relative rates of substituted *N*-ethylanilines on the competitive reactions.



17 **18** (3)

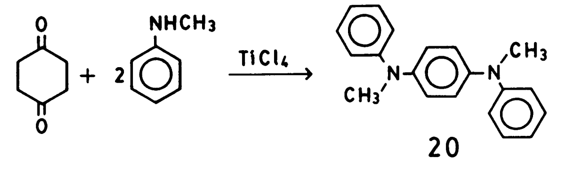
The formation of **18** shows that an acetal exchange reaction occurred in these conditions. This may produce the 1,4-dione also, which could follow the reaction in Eq. 2, because no monoenamine was obtained even if the amine was used in large excess. On the other hand, the reaction of pyrrolidine with **17** has been reported[3] to produce the corresponding enamine **19**. In an effort to determine the effect of the catalyst, this reaction was further studied, but the same results were obtained regardless of the presence of the acid.



19 (4)

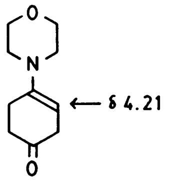
These results show that the conjugate acid of the aromatic amine is an active catalyst for the acetal-exchange reaction in these conditions but that the conjugate acid of the aliphatic amine has no or very little effect.

In spite of above results, an aromatic amine also produced a phenylenediamine derivative, as suggested in Eq. 1, if the reaction was carried out in the presence of $TiCl_4$. Under these conditions *N*-methylaniline gave *N*,*N′*-dimethyl-*N*,*N′*-diphenyl-*p*-phenylenediamine (**20**).



(5)

NMR Spectra of the Reaction Mixtures. In order to understand the differences between aromatic amine- and aliphatic amine-condensation processes, the reactions of **1** with some aliphatic or aromatic amine were followed by ^{1}H-NMR spectra of the reaction mixtures in sealed tubes under nitrogen. The spectra of the mixture of **1** and morpholine showed signals at δ 5.01 and at δ 2.13 due to the vinyl protons of the dienediamine **2** and its methylene protons and the vinyl proton of monoenamine **21** at δ 4.21. The signals due to **2** became progressively stronger as the reaction time, while those due to **21** disappeared after 4 h at 120 °C. When the sample was permitted to stand for 1 h in contact with air after the reaction, the signals due to **2** disappeared too and those due to aromatic protons of **3** appeared. ^{1}H-NMR spectra of the mixture of **1** with *N*-methylcyclohexylamime showed also signals due to the vinyl proton of monoenamine **22** at δ 4.22 along with those due to the corresponding dienediamine at δ 5.08.



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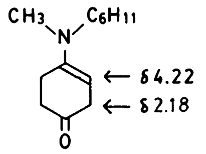
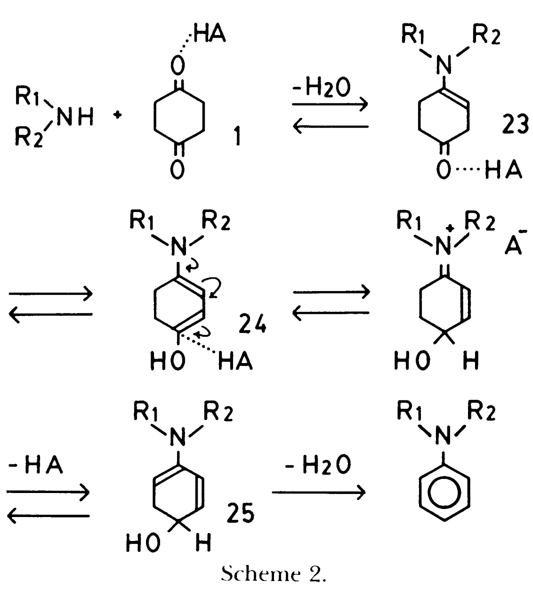


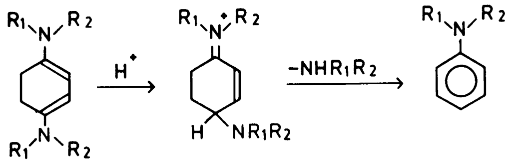
22

These facts show that the aliphatic amines reacted stepwise to the carbonyl groups of the 1,4-dione and that the intermediate monoenamines were produced in measurable amounts. On the contrary, ^{1}H-NMR spectra of the reaction mixture of *N*-methylaniline and **1** show the signals due to starting materials and those due to *N*-methyl-*N*-phenylaniline, but no signal ascribable to any intermediate.



Scheme 2.

Reaction Mechanism. On the basis of the above results, the mechanism shown in Scheme 2 is proposed for the reaction of aromatic amines with the 1,4-dione catalyzed by *p*-toluenesulfonic acid. The key steps in Scheme 2 are the enolization of monoenamine **23** and the protonation to γ-position of 24. These processes and the dehydration of **25** may be fast, because no intermediate was observed by ^{1}H-NMR spectroscopy. An alternate path which involves elimination of an amine from the dienediamine can also be considered (Eq. 6):



(6)

If the reaction proceeds *via* the dienediamine, the signals of the monoenamine should be observed at least in an early period of the reaction; this is because the reactivity of the residual carbonyl of the monoenamine **23** to the secondary aromatic amine should not be much greater than that of the starting ketone (**1**). Moreover, 2,6-dimethyl-1,4-cyclohexanedione (**8**) is very unlikely to produce any dienediamine because of its steric hindrance: therefore, the formation of **16** in Eq. 2 supports also Scheme 2. The discrepancy between the results of Fig. 1 and Table 1 is discussed below on the basis of the proposed mechanism.

Although there have been a number of examples of enamine formation, the mechanistic studies have been limited to the enamines derived from aliphatic amines. The addition step of aminoalcohol formation has been generally shown[3] to be noncatalytic. However, the addition reaction of weak bases such as semicarbazides or primary aromatic amines to carbonyl compounds is catalyzed by general acid catalysis. Since the addition step of the enamine formation is the same as that of the formation of the carbon nitrogen double bond, the addition of aromatic amines to **1** must occur by the general acid-catalysis. Consequently, essentially every step of the reaction in Scheme 2 is acid-catalyzed. Therefore, it is necessary to take into account not only the nucleophilicity of the amine, but also the acidity of the catalyst for discussion of the reactivity. In practice, the reactions with aromatic amines did not proceed without the acid catalyst. *p*-Toluenesulfonic acid was employed as the catalyst for the all experiments. HA in Scheme 2, then, is the conjugate acid of the amine in the mixture, and its acidity can be assumed to have a reverse tendency to the nucleophilicity of the amine. Therefore the ease of the reaction of the *N*-ethylaniline substituted with an electron-withdrawing group can be interpreted in terms of the increased acidity of its conjugate acid. The facility of the triphenylamine formation in Eq. 2 is also explained by the same reason. As seen in Fig. 1, two competitive reactions in a mixture were catalyzed by the same system, where the main acid was the conjugate acid of the more basic amine. Therefore, only nucleophilicity of the amine contributed to the relative reactivity on competitive reactions.

The fact that the condensation of **1** with aliphatic amines produced dienediamines but no tertiary monoamines is also explained by the same factor. The conjugate acids of aliphatic amines are so weak that the enolization of **23** and the protonation to 4-position of **24** are difficult. On the contrary, the formation of **23** and further addition of the aliphatic amine to the residual carbony of **23** must proceed smoothly, because the aliphatic amines react even without the acid catalyst.

On the other hand, the formation of the dienediamine derived from *N*-methylaniline in Eq. 5 may be due to the fast addition of the amine to the carbonyl activated by $TiCl_4$.

Finally we add a few comments on the present reactions from the viewpoint of organic synthesis. The formation of tertiary amines from secondary aromatic amines with halobenzene requires drastic conditions. Therefore, *N*-phenylation by use of 1,4-cyclohexanedione is worthwhile because of its mild conditions. The conditions in Table 1 are not always the most suitable. For example, increase of the catalyst concentration or of the reaction period lead to good yield of the products. As the solvent, aromatic hydrocarbonds are more favorable than polar ones such as dioxane. The reaction became slower in polar solvents.

Experimental

General. Melting points were uncorrected. ^{1}H-NMR spectra were recorded on a JNM-C-60HL spectrometer with $(CH_3)_4Si$ as an internal standard. IR spectra were taken on a JASCO Model IR-G spectrophotometer. Mass spectra were measured on a Hitachi M-80 mass spectrometer. GLPC analyses were carried out by a Hitachi 163 gas chromatograph using 1-decene or phenanthrene as an internal standard.

Materials. *N*-Ethyl-*p*-chloroaniline was prepared following a method given in "Organic Sytheses"[4]: Yield 60%; bp 89—90 °C/2 Torr (1 Torr=133.322 Pa). *N*-Ethyl-*p*-nitroaniline was obtained from *p*-nitroaniline in a similar manner: Yield 48%; mp 96—97 °C. *N*-Ethyl-*p*-anisidine was prepared in three steps involving acetylation of *p*-anisidine, alkylation by use of methyl iodide in the presence of sodium ethoxide, and successive hydration in basic coditions. The total yield was 28%. Found: C, 71.87; H, 8.96; N, 9.05%. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26%. The derivatives of 1,4-cyclohexanedione were all prepared from diethyl 4,4-(ethylenedioxy)pimelate (**26**). The compound **26** was obtained from furfural and malonic acid in three steps according to reported pocedures[5]: Bp 134—136 °C/0.5 Torr (lit, 134 °C/0.3 Torr). Ethyl 5,5-ethylenedioxy-2-oxocyclohexanecarboxylate (**27**) was prepared from **26** according to the direction of Gardner[5]: Bp 120 °C/1 Torr (lit, 114 °C/0.5 Torr). 4,4-(Ethylenedioxy)cyclohexanone (**17**) was obtained from **27** by hydration in 5% aq KOH for 6 h at room temperature: Yield 80%; mp 70—72 °C (lit,[6] 68—70 °C). Found: C, 61.77; H, 8.01%. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74%. Ethyl 5,5-ethylenedioxy-1-methyl-2-oxocyclohexanecarboxylate (**4**) and 2-methyl-1,4-cyclohexanedione (**13**) were prepared by the method of Narang.[7] Compound **4** was obtained from **26** in 59% yield: mp 71—72 °C (lit, 72 °C). Compound **13** was obtained from **4** in two steps: Yield 60%; mp 47—48 °C (lit, 47 °C). All other reagents were commercially available and were used after purification, if necessary.

2,6-Dimethyl-1,4-cyclohexanedione (8). A mixture of **4** (10 g, 4.13×10^{-2} mol) and sodium ethoxide prepared from 0.95 g (4.13×10^{-2} mol) of sodium was refluxed in ethanol (20 cm^3) for 10 h. Toluene (20 cm^3) was added to the reaction mixture, and then ethanol was gradually distilled off. An additional 20 cm^3 of toluene was added into the residue and the mixture was refluxed for 5 h. Methyl iodide (5.9 g, 4.15×10^{-2} mol) was then added at 0 °C and the mixture was allowed to stand overnight at room temperature. The mixture was refluxed for 2 h, and decomposed with 5% sodium carbonate solution (16 cm^3) and extracted with benzene. The extract was evaporated and the residue was distilled *in vacuo* to afford 6.3 g (60%) of ethyl 1,3-dimethyl-5,5-ethylenedioxy-2-oxocyclohexanecarboxylate (**6**): Bp 125 °C/1 Torr. The product (6.1 g, 2.4×10^{-2} mol) was refluxed with a mixture of 10% aqueous potassium hydroxide (30 cm^3) and ethanol (10 cm^3) for 10 h. The mixture was extracted with ether and evaporated *in vacuo*, giving 3.6 g (82%) of 2,6-dimethyl-4,4-(ethylenedioxy)cyclohexanone (**7**). The crude product (3.5 g, 1.9×10^{-2} mol) was warmed in 3 mol dm^{-3} hydrochloric acid (18 cm^3) at 80 °C for 1 h. Upon cooling to room temperature, a part of the product crystallized out of the solution, and was filtered. The filtrate was extracted with benzene and the extract was evaporated. The residue was combined with the above crystals and was recrystallized from hexane, affording 2.4 g (90%) of 2,6-dimethyl-1,4-cyclohexanedione: Total yield based on **4** is 44%; mp 84—86 °C; IR (KBr) 1707, 1142 and 2800—3000 cm^{-1}; NMR (CCl_4) δ=1.00—1.30 (6H, dd) and 1.80—3.00 (6H, m). Found: C, 68.75; H, 8.95%. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63%.

Condensation of 1,4-Cyclohexanediones and Secondary Aromatic Amines. The general procedure consists of a heating of 1,4-cyclohexanedione (0.5 g, 4.46×10^{-3} mol) with an equivalent of the amine and *p*-toluenesulfonic acid (20 mg) using toluene (30 cm^3) as the solvent in nitrogen atmosphere. The mixture was refluxed for 12 h under a Soxhlet extractor packed with $CaCl_2$ as desiccant, and the solution freed of the solvent *in vacuo*. The product was isolated by column chromatography on sillica gel eluted with hexane. The *N*-ethyl-*N*-phenylanilines obtained are summarized in Table 1. Some other tertiary amines obtained and their properties are presented below.

N-Methyl-*N*-phenylaniline (**10**) was obtained as a light yellow liquid from **1** and *N*-methylaniline in 77.2% yield: NMR (CCl_4) δ=3.25 (3H, s) and 6.63—7.28 (10H, m); MS, *m/z* 183 (M$^+$).

N-Methyl-*N*-phenyl-*m*-toluidine (**12**) was obtained as a light yellow liquid in 62.3% yield from **1** and *N*-methyl-*m*-toluidine, or in 61.6% yield from 2-methyl-1,4-cyclohexanedione and *N*-methylaniline: NMR (CCl_4) δ=2.28 (3H, s), 3.28 (3H, s) and 6.53—7.30 (9H, m); IR (neat) 1590, 1490, 750 and 690 cm^{-1}; MS, *m/z* 197 (M$^+$).

Triphenylamine (**15**) was obtained as crystals in 88.2% yield from **1** and diphenylamine: Mp 125—126 °C (from hexane).

3,5-Dimethyltriphenylamine (**16**) was obtained as crystals from 2,6-dimethyl-1,4-cyclohexanedione and diphenylamine in 28.9% yield: Mp 130—132 °C (from hexane); NMR (CCl_4) δ=2.20 (6H, s) and 6.45—7.35 (13H, m); IR (KBr disk) 1585, 1490, 755 and 690 cm^{-1}; MS, *m/z* 273 (M$^+$).

Competitive Reaction. A mixture of *N*-ethylaniline and another appropriate amine was used in the place of the amine component of the condensation described above. The competitive reaction was followed by gas chromatography every half hour until one of the amines gave 10% conversion. The relative rate (k_x/k_y) in Fig. 1 was determined from the ratios of the two products.

The Condensation of 4,4-(Ethylenedioxy)cyclohexanone (17) with N-*Methylaniline.* The method used here was virtually identical with that for 1,4-cyclohexanedione, but the latter was replaced with **17**. *N*-Methylaniline (0.35 g, 3.3×10^{-3} mol) and 0.5 g (3.2×10^{-3} mol) of **17** were refluxed in toluene (30 cm^3) in presence of *p*-toluenesulfonic acid (20 mg). After 30 h, GLPC analysis showed that *N*-methyl-*N*-phenylaniline and diacetal **19** were produced in an approximately equal yield (9%).

Condensation of 17 and Pyrrolidine. The procedure was similar to that of Stork[3] except that 2×10^{-2} equivalent *p*-toluenesulfonic acid to pyrrolidine was added. The pyrrolidine enamine of **17** was produced in 82% yield: Bp 135—137 °C/3 Torr (lit, 110—120 °C/0.1—0.15 Torr); IR 1640, 1115, 1055, and 850 cm^{-1}.

Condensation of 1 and N-Methylaniline in Presence of TiCl$_4$. To a mixture of *N*-methylaniline (5.8 g, 5.42×10^{-3} mol) and **1** (1.0 g, 8.9×10^{-3} mol) in benzene (44 cm^3) a benzene solution (9 cm^3) containing $TiCl_4$ (1.88 g) was added during 20 min at below 10 °C in nitrogen atmosphere with stirring. Then the mixture was stirred for 12 h at room temperature, the precipitate was filtered, and the filtrate was evaporated. The residue was crystallized from ethanol, affording *N,N'*-dimethyl-*N,N'*-diphenyl-*p*-phenylenediamine (0.7 g, 27%) as crystals: Mp 149—150 °C; IR 1590, 1500, 860, and 840 cm^{-1}. Found: m/z 288.1614. Calcd for $C_{20}H_{20}N_2$: M, 288.1625.

The authors wish to thank Mr. Katsumasa Iwaya for obtaining some of the NMR spectra and Miss Machiko Nozawa for the preparation of the derivatives of 1,4-cyclohexanedione.

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