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The Reaction of β-Amino α,β-Unsaturated Esters with Amines

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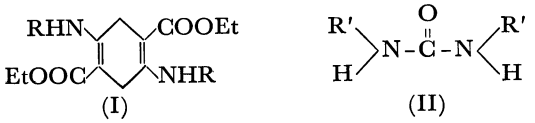
The reactions between amines and 1,4-bis(ethoxycarbonyl)-2,5-bis(alkyl- or arylamino)-1,4-cyclohexadiene(I) and its analogs are studied. The main products are *N,N'*-disubstituted urea(II) and 1,4-bis(alkyl- or arylamino)-1,4-cyclohexadiene(V) instead of the expected carboxamide. The presence of small amounts of ethyl *N*-substituted carbamate (III) in the products leads to the conclusion that the reaction proceeds through two successive steps: the nucleophilic attack by an amine upon a carbonyl carbon atom of the ethoxycarbonyl group, with a cleavage of a carbon-carbon bond to give III and V, and the amidation of III *in situ*, giving II. The rate of the second step is much faster than that of the first step. The formation of II occurs in the compounds with a β-amino α,β-unsaturated carbonyl group.

The treatment of carboxylic esters with amines is known to be a convenient method for the preparation of carboxamides. However, the reactions between 1,4-bis(ethoxycarbonyl)-2,5-bis(alkyl- or arylamino)-1,4-cyclohexadiene(I) and amines give *N,N'*-disubstituted urea(II), but none of the expected carbxamide.



(I) (II)

a: $R=R'=CH_3(CH_2)_4-$
b: $R=R'=C_6H_5-$

Similar results have been reported by Roberts and Edwards[1] in the reaction of ethyl β-anilinocrotonate (VI) with aniline. While this type of the reaction is expected to occur generally in compounds with a β-amino α,β-unsaturated carbonyl group, no details of the reaction mechanism have been reported. In this paper, the reaction pathway will be elucidated and the reaction mechanism will be explained.

Results and Discussion

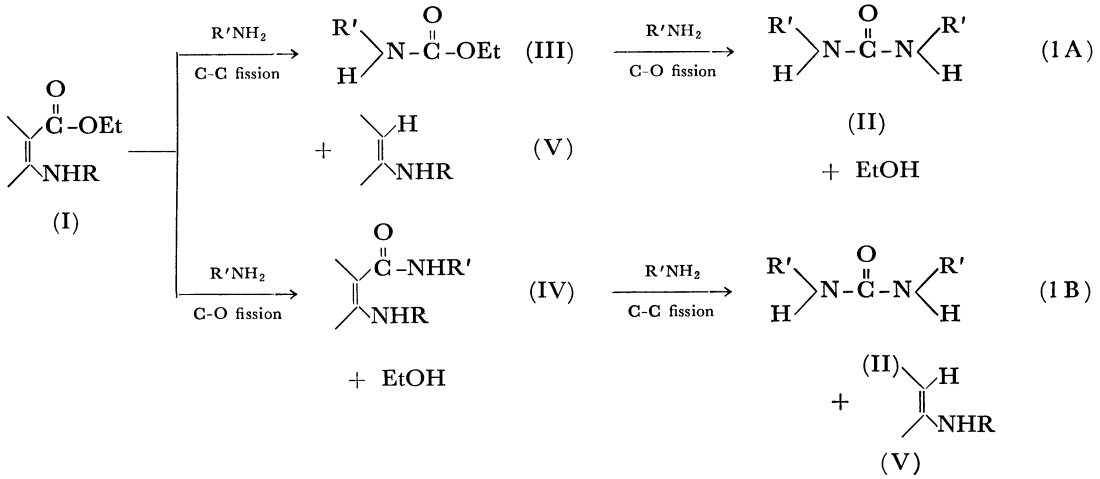
When Ia was heated with pentylamine at temperatures above 230°C in toluene, the reaction proceeded to a certain extent, thus giving *N,N'*-dipentylurea(IIa). The same reaction product was obtained in a good yield by the treatment of Ib with pentylamine. The absence of *N*-pentyl-*N'*-phenylurea and/or *N,N'*-diphenylurea in the products of the latter case excluded the possibility of the transfer of the RNH- group in I to the product during the reaction.

The formation of II might result from the transfer of the carbonyl group from I to the amine used in the reaction. There are two possible pathways, depending on whether the cleavage of the C–C or that of the C–O bond takes place first, as is represented in Scheme 1.

Roberts and Edwards[1] assumed that the cleavage of ethyl β-anilinocrotonate(VI) with aniline took place through the route shown in (1B), but the presence of an intermediate (IV) has not yet been confirmed. The analyses of the reaction products obtained by keeping a mixture of Ib and aniline for 1 hr at 230°C in toluene revealed the presence of small amounts of ethyl *N*-phenylcarbamate(III), but an absence of the carboxamide(VI). The same analytical results were obtained for the reaction products of VI with aniline. In both reactions, the formation of decarboxylated products was detected. The formation of IIb by the treatment of III with aniline was also confirmed. The reactions, therefore, must proceed along the route shown in (1A).

The overall rate of this reaction was mostly controlled at the steps from I to III, since the yield of II from III was four times that from I under the same reaction conditions.

1) R. M. Roberts and E. B. Edwards, *J. Amer. Chem. Soc.*, **72**, 5537 (1950).



Scheme 1.

Table 1. Effects of the pK_a values of amines on the yield of *N,N'*-disubstituted urea[a)]

Amines; RNH_2 R	pK_a [b)]	Product	Mp (°C)	Yield (%)	$k_2 \times 10^4$ [c)] (sec^{-1})
$CH_3(CH_2)_4$-	10.63	*N,N'*-dipentylurea	97—100	31.7	12.9
p-$CH_3OC_6H_4$-	5.34	*N,N'*-bis(4-methoxyphenyl)urea	229—230	15.0	5.17
p-$CH_3C_6H_4$-	5.10	*N,N'*-di-*p*-tolylurea	257—258	10.9	3.48
C_6H_5-	4.60	*N,N'*-diphenylurea	242	8.85	2.98
p-ClC_6H_4-	3.98	*N,N'*-bis(4-Chlorophenyl)urea	278—279	8.48	2.87
m-$CH_3C_6H_4$-	4.72	*N,N'*-di-*m*-tolylurea	215—217	6.20	2.06
m-ClC_6H_4-	3.50	*N,N'*-bis(3-chlorophenyl)urea	242—244	3.26	0.90

a) Reaction conditions: A solution of 1.00×10^{-2} mol of amine and 2.46×10^{-3} mol of Ib in 10 ml of toluene was heated at 230±1°C for 1 hr.

b) Taken from: S. Patai, "The chemistry of the amino group", Interscience Publishers, New York, N. Y. (1968), p. 174, 182.

c) Calculated from an integrated form of bimolecular rate equation as below;

$$k_2 = 1/[C_0 t(M-2)]\times\ln(M-2Y)/M(1-Y)$$

Y: Yield of II in a period of first 1 hr, M: Initial molar ratio of reactants; [amine]/[(I)], C_0: Initial molar concentration of I, t: reaction time; 3.6×10^3 sec.

The effects of the pK_a values of amines on the reaction rate were investigated in the reactions of Ib with various amines. The yields and rate constants roughly evaluated by fitting the integrated form of the bimolecular rate equation to the yields are listed in Table 1. The reactivity of the amines examined increased with the increase in their basicity, and the logarithm of the rate constants fell near a line when plotted against the pK_a values of the corresponding amines (Fig. 1). The reaction appeared to be a nucleophilic substitution at the carbonyl carbon atom involving slow C–N bond formation, followed by a relatively fast C–C bond fission proceeding through a tetrahedral intermediate.

The rate of the reaction was also affected by the nature of the substituent(R) on the nitrogen atom of I. The yields of IIb in reactions between aniline and various *N*-substituted I are shown in Table 2. The yields increased in the order of: R=alkyl, H, aryl; this order was the reverse of that of the basicity of amines, RNH_2. The electron density on the carbonyl carbon atom in I increases with the increase in the electron-donating effect of the RNH– group exerted through the double bond, inhibiting the nucleophilic attack of $R'NH_2$.

To gain insight into the factors which govern the

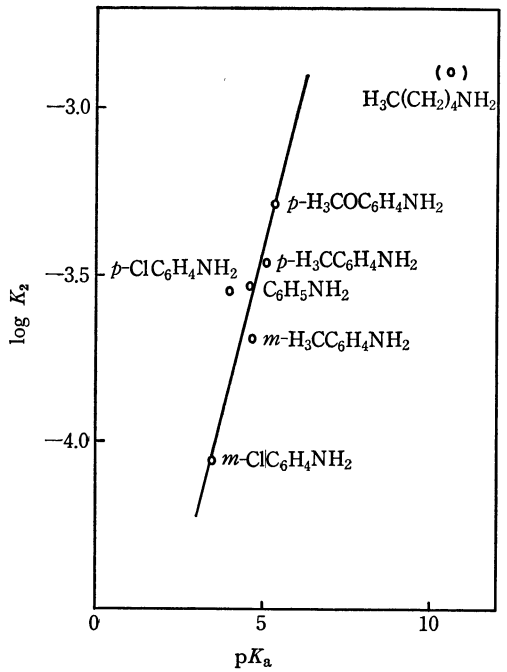


Fig. 1. The relation between the apparent second-order rate constant (k_2) and the pK_a values of amines.

TABLE 2. THE YIELD OF *N,N'*-DIPHENYLUREA BY THE REACTION BETWEEN ANILINE AND I[a]

R	RHN, COOEt, EtOOC, NHR	pK_a value of RNH_2[b]	Yield of *N,N'*-diphenylurea (%)
$CH_3(CH_2)_4$-	(Ia)	10.63	2.0
C_6H_5-	(Ib)	4.60	27.4
p-$CH_3C_6H_4$-	(Ic)	5.10	27.2
p-ClC_6H_4-	(Id)	3.98	28.1
p-$CH_3OC_6H_4$-	(Ie)	5.34	26.0
H-	(If)	9.24	5.9

a) Reaction conditions: A solution of 8.0×10^{-2} mol of aniline and 1.0×10^{-2} mol of I in 40 ml of toluene was heated at 230±2°C for 1 hr.
b) Taken from: S. Patai, "The chemistry of the amino group", Interscience Publishers, New York, N. Y. (1968), pp. 174, 182.

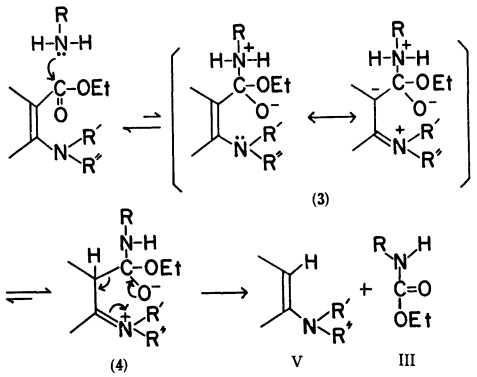
facile C–C bond cleavage, various types of β-anilino α,β-unsaturated carbonyl compounds were subjected to reactions with aniline. The results are summarized in Table 3. The C–C bond cleavage occurred not only in β-anilino α,β-unsaturated carboxylic esters, but also in the β-anilino α,β-unsaturated ketone. On the other hand, the compounds in which the α,β-double bond is incorporated with an aromatic system gave neither II nor amide.

Aliphatic β-amino α,β-unsasurated carbonyl compounds exist exclusively in the enamine form[2] and are capable of reaction with an electrophile on nitrogen or on an α-carbon atom, as is shown by the mesomeric forms, (1) and (2):

(1) (2)

The electron-donating sites in enamines may take part in the proton-transfer step in the reaction pathway, directing the reaction to the fission of the C–C bond instead of the C–O bond.

The proposed reaction mechanism is shown in Scheme 2.



Scheme 2.

The ammonium hydrogen in (3) transfers either to the carbon atom or to the nitrogen atom, instead of to the ethoxyl oxygen atom, as is the case with an ordinary amidation.

TABLE 3. REACTIONS BETWEEN ANILINE AND β-ANILINO α,β-UNSATURATED CARBONYL COMPOUNDS

Compounds		mol	Aniline mol	Solvent toluene (ml)	Reaction conditions Temp(°C)	Time(min)	Product	Yield (%)
CH_3-C(NHPh)=CH-COOEt	(VI)	9.3×10^{-3}	4.3×10^{-3}	10	230±2	60	*N,N'*-diphenylurea	27.0
CH_3-C(N(Me)Ph)=CH-COOEt	(VII)	4.3×10^{-3}	2.2×10^{-2}	10	230±2	60	*N,N'*-diphenylurea	23.0
CH_3-C(NHPh)=C(CH_2CH_3)-COOEt	(VIII)	4.6×10^{-3}	2.2×10^{-2}	10	235±2	60	*N,N'*-diphenylurea	45.0
CH_3-C(NHPh)=CH-CO-CH_3	(IX)	4.6×10^{-3}	2.2×10^{-2}	10	230±2	120	acetanilide	27.8
EtOOC, NHPh, PhHN, COOEt	(X)	2.5×10^{-3}	1.1×10^{-1}	—	217±2	120	2,5-dianilinoterephthalic acid, ethyl hydrogen 2,5-dianilinoterephthalate, *N*-ethylaniline	17.4, 37.7, 36.5[a]
COOEt, NHPh	(XI)	1.8×10^{-3}	1.1×10^{-1}	—	230±2	120	2-anilinobenzoic acid	trace

a) Estimated by the area of the peak in glc.

2) G. O. Dudek and R. H. Holm, *J. Amer. Chem. Soc.*, **83**, 2099 (1961).

In the case of enamines, protonation takes place rapidly on nitrogen and is followed by a transfer of the proton to the carbon.[3] Therefore, the final product of the proton-transfer step is presumably a C-protonated step (4), which gives III and V through the C–C bond cleavage. The resulting III was then considerably quickly converted to II by the reaction with the excess amine presented.

Experimental

The infrared spectra were recorded on a Hitachi EPI-G3 spectrometer. The analyses of the volatile substances were carried out by means of a Hitachi Model 063 gas chromatograph equipped with a thermal conductivity cell. A 100× 0.5 cm packed column of Apiezon L (25%) on Chromosorb-W was used at a flow rate of 40 ml/min of He gas. For thin-layer chromotagraphy (tlc), a plate of Silica-gel HF (E. Merk Co.) was used. Plates were developed with Solvent 1 (ether/hexane=20/30) or Solvent 2 (benzene/tetrahydrofuran/acetic acid=25/25/1). For column chromatography, a column of 20×1.8 cm was prepared by slurrying silica gel (Wako Gel C-200, Wako Chemical Co.) in benzene for packing. The melting points and boiling points were not corrected.

Materials. All the reagents except those listed below were obtained from commercial sources and were used without further purification. The aniline, pentylamine, and toluene were dried over synthetic zeorite (Zeorum A-4, Tekkosha Co.) and distilled before use. The solid amines listed in Table 1 were purified by recrystallization. The ethyl *o*-anilinobenzoate(XI) was purified by silica gel column chromatography before use. The 1,4-bis(ethoxycarbonyl)-2,5-bis(alkyl- or arylamino)-1,4-cyclohexadiene(Ia: mp 76—77°C, Ib: mp 164—165°C, Ic: mp 218—220°C, Id: mp 240—243°C, Ie: mp 187—188°C, If: mp 117—119°C)[4], the ethyl β-anilinocrotonate(VI)[1] (bp 116—122°C/3×10^{-2} mmHg), the ethyl β-(*N*-methylanilino)-crotonate(VII)[5] (bp 110—120°C/4×10^{-3} mmHg), the ethyl α-ethyl β-anilinocrotonate(VIII)[1] (bp 105—107°C/5×10^{-3} mmHg), the 4-anilino-3-penten-2-one(IX)[6] (mp 47—48°C), the diethyl 2,5-dianilinoterephthalate(X)[7] (mp 142—143°C), and the 1,4-cyclohexanedione[8] (mp 71—73°C) were prepared by published procedures.

Reactions. *a) Ia with Pentylamine*: In a glass ampoule, 1.0 g (2.5 mmol) of Ia, 0.78 g (10 mmol) of pentylamine, and 10 ml of toluene were placed. The free space was filled up with nitrogen before the ampoule was sealed. The ampoule was then heated at 230°C for 1 hr in an oil bath. The contents of the ampoule were subsequently transferred to a flask and were concentrated to half of their original volume. The crystals which appeared were collected by filtration, washed with cold ethanol, and dried in a vacuum to give 0.017 g of IIa, which was confirmed by a comparison of its IR spectrum with that of an authentic sample prepared from urea and pentylamine.[9] Recrystallization from ethanol gave an analytically pure sample: mp 98—100°C, Found: C, 66.01; H, 12.07; N, 13.92%. IR(cm^{-1}): 3345(–NH–), 2960(–CH_3), 2925(–CH_2–), 1625, 1580, and 1276 (amide).

b) Ib with Pentylamine: From 1.00 g (2.46 mmol) of Ib, 0.87 g (10 mmol) of pentylamine, and 10 ml of toluene, 0.226 g of white crystals was obtained by the procedure described in *a)*. The product was determined to be IIa by a mixed-melting-point determination with an authentic sample.

c) Ib with Aniline. A mixture of 1.00 g (2.46 mmol) of Ib, 0.93 g (10.0 mmol) of aniline, and 10 ml of toluene was heated at 230°C in a way similar to that described in *a)*. A white precipitate which separated when the reaction mixture was brought to room temperature was collected by filtration, washed with 10 ml of cold toluene, and dried in a vacuum to give 0.09 g of IIb, which was confirmed by a comparison of its IR spectrum with that of an authentic sample. Recrystallization from toluene gave an analytical sample: mp 242°C, Found: C, 73.64; H, 5.75; N, 13.12%. IR (cm^{-1}): 3325 and 3280(–NH–), 1652, 1557, and 1319 (amide), 755 and 695(phenyl).

A small portion of the filtrate was freed from aniline and toluene under reduced pressure. The residue was dissolved in 1 ml of benzene and was then placed at the top of the column. Elution was achieved with 100 ml portions of each of the following series of solvents: benzene, benzene/ether=80/20, benzene/ether=50/50, ether, and methanol. About 90 fractions of 5 g each were collected. The constituents of each fraction was determined by tlc. Fractions 1—4 gave nothing. Fractions 5—8 gave a mixture of two substances, which appeared at the R_f value of 0.61 (Compound A) and 0.58 (Compound B) in tlc (Solvent 1). The isolation of each compound was achieved by preparative tlc. Compound A (red crystals, mp 141—142°C) was found to be completely identical with X by IR spectroscopic analysis and by a mixed-melting-point determination with an authentic sample. Compound B [brown oil, IR(cm^{-1}): 3390 and 3350(–NH–), 1690, 1256, and 1216(ester), 1602 and 1500(C=C, aromatics), 1317(C–N), 745 and 700(phenyl)] was assumed to be ethyl 2,5-dianilinobenzoate(XII) on the basis of its IR spectrum, which was almost the same as that of *N,N'*-diphenyl-*p*-phenylenediamine(XIII) except for additional absorptions suggesting the presence of an ester group in the molecule. Fractions 9—14 showed a single spot on tlc (Solvent 1). The removal of the solvent from it gave a light yellow oil. The compound changed spontaneously to brown solids upon contact with air. Recrystallization from benzene gave pale gray crystals: mp 146—150°C. IR(cm^{-1}): 3390(–NH–), 1602 and 1500(C=C, aromatics), 1317(C–N), 822(*p*-disubstituted benzene), 745 and 700(phenyl). Its IR spectrum and the R_f value of tlc completely matched those of an authentic sample of *N,N'*-diphenyl-*p*-phenylenediamine. Since compounds with a cyclohexadiene ring are easily converted to aromatic compounds when they are brought into contact with air in the presence of the solvent, X, XII, and XIII were supposed to have been derived from Ib, 1-ethoxycarbonyl-2,5-dianilino-1,4-cyclohexadiene(XIV), and 1,4-dianilino-1,4-cyclohexadiene(Va) respectively, all of which existed in the original reaction products. The formation of XIII by the treatment of air with the Schiff's base obtained from 1,4-cyclohexanedione and aniline was confirmed by a separate experiment. Thus, the decarboxylation of Ib resulting in a Schiff's base (Va) was indirectly confirmed. Fractions 15—26 gave practically nothing. Fractions 27—32 showed a single spot on tlc (Solvent 1). The removal of the solvent from any one of them gave a thick oil which solidified on standing in a refrigerator. Recrystallization from ethanol gave white crystals: mp 51—53°C, IR(cm^{-1}):

3) E. J. Stamhuis and W. Mass, *J. Org. Chem.*, **30**, 2156 (1965).
4) F. Higashi, A. Tai, and K. Adachi, *J. Polym. Sci. Part A*-1, **8**, 2563 (1970).
5) A. Risaliti and P. Bruni, *Ann. Chem.*, (Rome), **53**, 595 (1963).
6) E. Roberts and E. E. Turner, *J. Chem. Soc.*, **1929**, 1832.
7) A. Tai, F. Higashi, and S. Yokomizo, *J. Polym. Sci. Part A*-1, **9**, 2481 (1971).
8) W. G. Dauben, "Organic Syntheses," **45**, p. 25, (1965).
9) T. L. Davis and K. Blanchard, *J. Amer. Chem. Soc.*, **45**, 1817 (1923).

3315(-NH-), 3050(aromatics), 2975(aliphatics), 1722, 1240, and 1060(ester), 1705, 1540, and 1320(amid), 750 and 695 (phenyl). With respect to the IR spectrum, the R_f value of tlc, and the mixed-melting-point determination, the compound was identical with an authentic sample of ethyl *N*-phenylcarbamate(III). Fractions 33—36 gave a mixture of aniline, III, and IIb. Fractions 37—39 gave IIb. Fractions 40—62 gave nothing. Fractions 63—70 gave deep red crystals, which were identical with ethyl hydrogen 2,5-dianilinoterephthalate in IR spectrum and in the R_f value of tlc. This compound was expected to have been converted X, which existed in Ib as an impurity. The details of the reaction products between aniline and X are described in *j*). Fractions 71—90 gave practically nothing.

d) Ib with Various Amines. The amounts of reagents in each run were adjusted to 2.46 mmol of Ib, 10 mmol of amines, and 10 ml of toluene. The reaction were carried out at 230°C for 1 hr. The resulting *N,N'*-disubstituted urea was isolated from the reaction products by the process described in *a*). The yields and products of each run are listed in Table 1.

e) Various I Substances with Aniline. The reactions were carried out in the way described in *a*). The yield of IIb in each run is listed in Table 2.

f) VI with Aniline. A mixture of 1.9 g of VI, 4.0 g of aniline, and 10 ml of toluene was heated in a way similar to that described in *a*). IIb(0.53 g) was separated from the reaction products. The distillation of the filtrate gave three fractions; bp 35—40°C/50 mmHg(toluene), bp 78—82°C/13 mmHg, and nonvolatile substances. The gas chromatogram(at 150°C) of the fraction at bp 78—82°C/13 mmHg showed two peaks, at R_t=2.2 min and 4.1 min. The former peak was identical with that of aniline, while the latter peak was matched that of the anil of acetone prepared by the method of Kuhn and Schretzmann.[10] The tlc(Solvent 1) of the nonvolatile substance showed a big spot at R_f=0.55. The isolation of this substance by preparative tlc gave light yellow crystals. The IR spectrum, mp, and R_f value of this compound were identical with those of an authentic sample of III.

g) Other β-Anilino α,β-unsaturated Carboxylic Acid Esters with Aniline. In a way similar to that described in *a*), VII and VIII were subjected to a reaction with aniline. The results are listed in Table 3.

h) IX with Aniline. The reaction was carried out in a manner similar to that in the case of I. The tlc(Solvent 1) of the products showed a big spot (R_f=0.04). The compound corresponding to this spot was isolated by preparative tlc and was determined to be acetanilide by an IR spectroscopic analysis and by a mixed-melting-point determination with an authentic sample. From one-twentieth of the product, 10.7 mg of acetanilide were obtained as crystals; mp 112—114°C.

i) III with Aniline. A mixture of 1.0 g of III, 2.2 g of aniline, and 10 ml of toluene was subjected to a reaction under the same conditions as in *a*). IIb was thus obtained in a yield of 0.50 g. (39%).

j) X with Aniline. Since the reaction between X and aniline in the presence of the solvent (toluene) was slow, the reaction was carried out in the absence of the solvent. Thus, a mixture of 1.0 g of X and 19 ml of aniline was heated for 2.0 hr at 220°C in a sealed tube. The product was then roughly divided into a nonvolatile solid and a volatile liquid by vacuum distillation. The solid was composed of three substances, which appeared at R_f values of 0.66 (Compound A), 0.46 (Compound B), and 0.37 (Compound C) in tlc(Solvent 2). Each compound was isolated by preparative tlc and its structure was determined by IR spectroscopic and elemental analysis to be as follows: Compound A: unchanged X; Compound B: ethyl hydrogen 2,5-dianilinoterephthalate, Found: C, 68.67; H, 5.43; N, 7.39%. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44%. IR(cm^{-1}), 3360(-NH-), 1698, 1264, and 1160 (ester), 1668 and 1540 (-COOH), 750 and 694(phenyl); Compound C: 2,5-dianilinoterephthalic acid, Found: C, 66.01; H, 4.72; N, 7.63%. The IR spectrum of this compound was identical with that of a saponification product of X. The gas chromatogram of the volatile liquid obtained at 120°C showed two peaks, corresponding to aniline (R_t=1.5 min) and *N*-ethylaniline (R_t=2.7 min) respectively.[11] The structure of the latter compound was confirmed by a study of its IR spectrum.

k) XI with Aniline. Acid-freed XI (1.0 g) and aniline (10 ml) were heated for 2 hr at 230°C in a sealed tube. The tlc (Solvent 2) of the product showed two prominent spots, at R_f 0.62 (aniline) and 0.78(XI), and one weak spot, at R_f 0.64(2-anilinobenzoic acid). No further treatment of the product was undertaken.

10) R. Kuhn and H. Schretzmann, *Chem. Ber.*, **90**, 557 (1957).

11) It has been reported that alkyl-oxygen fission in the hydrolysis of esters might occur if the carbonium ion to be formed is sufficiently stable[12] or if the rate of the $B_{AC}2$ reaction of the ester is remarkably diminished by steric hindrance.[13] In this reaction, it may be considered that the nucleophilic attack of aniline molecules occurred hardly at all at the carbonyl carbon atom, but more at the alkyl carbon atom. Therefore, alkyl-oxygen fission occurred to form acid and *N*-ethylaniline. The further details of this reaction will be reported separately.

12) G. S. Hammond and J. T. Rudesill, *J. Amer. Chem. Soc.*, **72**, 2769 (1950).

13) L. R. C. Barclay, N. D. Hall, and G. A. Cooke, *Can. J. Chem.*, **40**, 1981 (1962).