Kinetics of the Reaction of Some 3- and 5-Substituted 2-Furoyl and *ortho*- and *para*-Substituted Benzoyl Chlorides with *m*-Chloroaniline in Benzene

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The rate of the reactions of some 3- and 5-substituted 2-furoyl chlorides and corresponding *ortho*- and *para*-substituted benzoyl chlorides with *m*-chloroaniline in benzene was measured. The log *k* values at 25° were correlated with Brown's σ^+ constants and a slope greater than that for benzoylation was found. The results are in agreement with a two-step S_AN mechanism where the rate-determining step is the attack of the lone pair of the electrons of the amino-group on the carbonyl carbon atom. A variable σ^+ value for the 2-furyl group was obtained. The substituent in the 3-position in the furan ring does not exert a steric effect on the rate.

THE Hammett equation has been applied to reactions of five-membered heteroaromatic rings by considering the 2,4- and 2,5-positions as *meta*- and *para*-like, respectively, and then using σ_m and σ_p values. The differences between the resulting ρ values with those for the corresponding benzenoid side-chain reactions were discussed in terms of ' intensity of transmission of substituent effects.' The relative magnitudes of substituent effects in five-membered heteroaromatic rings vary according to the type of reaction. For side-chain reactions the order of sensitivity was found to be pyrrole > furan > selenophen > thiophen > benzene.[1-9]

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[1] H. H. Jaffé and H. L. Jones, *Adv. Heterocyclic Chem.*, 1964, **3**, 209.

[2] F. Fringuelli, G. Marino, and G. Savelli, *Tetrahedron*, 1969, **25**, 5815.

[3] T. A. Melent'eva, L. V. Kazanskaya, and V. M. Berezovskii, *Doklady Akad. Nauk S.S.S.R.*, 1967, **175**, 354 (*Chem. Abs.*, 1967, 120, 484).

[4] J. Tirouflet, *Adv. Polarography*, 1960, **1**, 740; J. Tirouflet and J. P. Chané, *Compt. Rend.*, 1965, **245**, 80; P. Fournari, Dissertation, Dijon, 1961.

[5] D. Spinelli, G. Guanti, and C. Dell'Erba, *Ricerca sci.*, 1968, **38**, 1048.

[6] W. K. Kwok, R. A. More O'Ferrall, and S. I. Miller, *Tetrahedron*, 1964, **20**, 1913.

[7] D. S. Noyce and G. V. Kaiser, *J. Org. Chem.*, 1969, **34**, 1008.

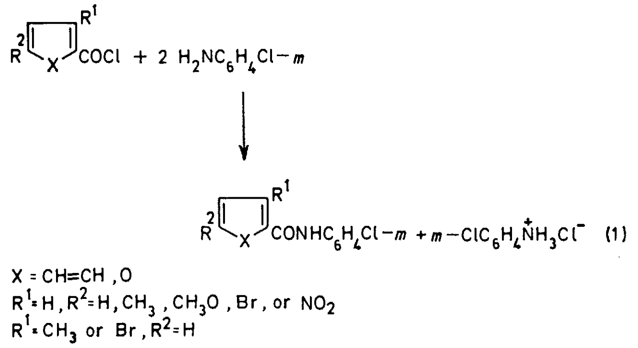
[8] D. S. Noyce, C. A. Lipinski, and R. W. Nichols, *J. Org. Chem.*, 1972, **37**, 26.

[9] D. S. Noyce and H. J. Pavez, *J. Org. Chem.*, 1972, **37**, 2620, 2623.

Recently Tomasik and Johnson [10] pointed out that it appears to be a more meaningful approach to consider the differences in the ρ values as representing non-additivity of substituent effects. The heteroatom was considered as a substituent replacing a vinyl group, –CH=CH–, in a benzene ring and able to interact *via* proximity effects with the side-chain, altering its susceptibility to substituent influences.

Previously we have studied the reactions of some 5- [11] and 3-substituted 2-thenoyl chlorides [12] with aniline in benzene. The results showed that the thiophen ring is more efficient than benzene in relaying the electronic effects of substituents to the reaction centre, and that 3-substituents in the thiophen ring did not exert a steric effect on the rate.

We now report a kinetic study of the reactions of some 3- and 5-substituted 2-furoyl chlorides and the corresponding *ortho*- and *para*-substituted benzoyl chlorides with *m*-chloroaniline in benzene with the aim of studying transmission of the electronic effects through the furan ring and the effect on the rate exerted by the 3-substituents.



RESULTS AND DISCUSSION

Table 1 reports the rate constants for the reaction of acid chlorides with *m*-chloroaniline in benzene. The reactions were followed kinetically as previously described [13,14] and excellent second-order kinetics were always obtained. The results show that electron-withdrawing substituents in the acid chloride increase the rate, whereas electron-donating groups lead to a decrease. The rate constants of 5-substituted 2-furoyl chlorides are slower than those of *para*-substituted benzoyl chlorides for electron-donating substituents and faster for electron-withdrawing groups. The values of the activation parameters are similar to those for benzoylation and show regular variation with the substituent in the acid chloride. The large negative entropies of activation are as expected for a highly polar transition state and similar to those found for reactions of thenoyl [11,13] and furoyl chlorides.[12,14]

TABLE 1

Second-order rate constants and activation parameters for the reaction of acid chlorides with *m*-chloroaniline

X-2-Furoyl chloride	10^2k/l mol^{-1} s^{-1} [a] 15 °C	25 °C	40 °C	log *A*	E_A [b]/ kcal mol^{-1}	ΔS [c]/ cal mol^{-1} K^{-1}
H [d]		0.74		3.98	8.33	−42.3
3-CH	0.28	0.48	0.92	3.86	8.44	−42.8
5-CH_3	0.12	0.19	0.43	4.17	9.38	−41.4
5-CH_3O	0·020	0.040	0.083	4.01	10.15	−42.2
3-Br	1.58	2.71	4.77	4.17	7.86	−41.4
5-Br	0.78	1.35	2.46	4.08	8.14	−41.8
5-NO_2	9.91	15.9	25.2	4.03	6.62	−42.1
X-Benzoyl chloride						
H [e]	0.24	0.42	0.81	3.97	8.67	−42.3
o-CH_3	0.17	0.30	0.62	4.13	9.09	−41.6
p-CH_3	0.13	0.21	0.47	4.10	9.21	−41.7
p-CH_3O	0.038	0.076	0.16	4.34	10.21	−40.6
c-Br	0.70	1.20	2.17	3.96	8.05	−42.4
p-Br	0.38	0.60	1.24	3.99	8.46	−42.2
p-NO_2	1.31	2.05	3.89	4.04	7.81	−42.0

[a] Rate constants are accurate to ±3%. [b] The estimated precision is *ca.* ±0.85 kcal mol^{-1}. [c] At 25°, the estimated precision is *ca* . ±3 cal mol^{-1} K^{-1}. [d] See ref. 1. [e] F. J. Stubbs and C. N. Hinshelwood, *J. Chem. Soc.*, 1949, S71, 10^2k_{25}/l mol^{-1} s^{-1} 0.436, E_A 9.27 kcal mol^{-1}.

We applied the Hammett equation, assuming that the 2,5-positions in the furan ring correspond to the *para*-position in the benzene ring and using σ_p values.[1] The plots of log *k* at 25° for the reactions of 5-substituted 2-furoyl chlorides and *para*-substituted benzoyl chlorides with *m*-chloroaniline against the σ_p constants [15] are linear with a slope of 2.21 (*r* 0.967) and 1.21 (*r* 0.951) respectively.

Better relationships are obtained for Brown's σ^+ constants [16] with a slope of 1.68 (*r* 0.999) and 0.91 (*r* 0.999) for reactions of furoyl and benzoyl chlorides, respectively (Figure 1). Previously log *k* at 25° for the reactions of benzoyl [17,18] and 2-thenoyl chlorides [11] with anilines were plotted against σ constants giving slopes of 1.22 (*r* 0.996) [17] and 1.42 (*r* 0.978) [18] for the reaction of benzoyl chlorides and 1.79 (*r* 0.991) for the reaction of 2-thenoyl chlorides.[11] Good relationships were obtained by plotting log *k* at 25° for the reactions of benzoyl and 2-thenoyl chlorides with aniline against σ^+ constants with slopes of 1.08 (*r* 0.997) and 0.92 (*r* 0.987) for reactions of benzoyl chlorides and 1.29 (*r* 0.984) for those of 2-thenoyl chlorides. The slope for the reaction of benzoyl chlorides with *m*-chloroaniline is similar to that of the reaction of benzoyl chlorides with aniline. The greater value of the rate sensitivity of the substituents in the 2-furoyl chloride reactions, by comparison with that for benzoylation and the 2-thenoyl chloride reactions

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[10] P. Tomasik and C. D. Johnson, *Adv. Heterocyclic Chem.*, 1976, **20**, 1.

[11] G. Alberghina, A. Arcoria, S. Fisichella, and G. Scarlata, *Gazzetta*, 1973, **103**, 319.

[12] G. Alberghina and S. Fisichella, *J.C.S. Perkin II*, 1978, 81,

[13] A. Arcoria and S. Fisichella, *J. Org. Chem.*, 1973, **38**, 3774.

[14] A. Arcoria, S. Fisichella, G. Scarlata, and D. Sciotto, *J. Org. Chem.*, 1974, **39**, 3025.

[15] J. E. Leffler and E. Grunwald, ' Rates and Equilibria of Organic Reactions ', Wiley, New York, 1963, p. 173.

[16] H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, 1958, **80**, 4979.

[17] E. G. Williams and C. N. Hinshelwood, *J. Chem. Soc.*, 1934, 1079.

[18] R. A. Benkeser, C. E. DeBoer, R. E. Robinson, and D. L. Sauve, *J. Amer. Chem. Soc.*, 1956, **76**, 628.

indicates that the furan nucleus is more efficient than benzene and thiophen in relaying the electronic effects of the substituents to the reaction centre. The higher value of the constant for the reaction of 5-substituted 2-furoyl chlorides with *m*-chloroaniline, compared with that for benzoylation and the 2-thenoyl chloride reactions can be ascribed to the diminished aromatic character of furan, as shown by the calculated atom localization energy of 2.4β, compared with 3.5β for thiophen and 4β for benzene.[6,19] The sequence of strength of transmission of substituent effects through five-membered heteroaromatic rings in the reactions of acid chlorides with anilines is furan > thiophen > benzene, similar to that found for other side-chain reactions.[1-9]

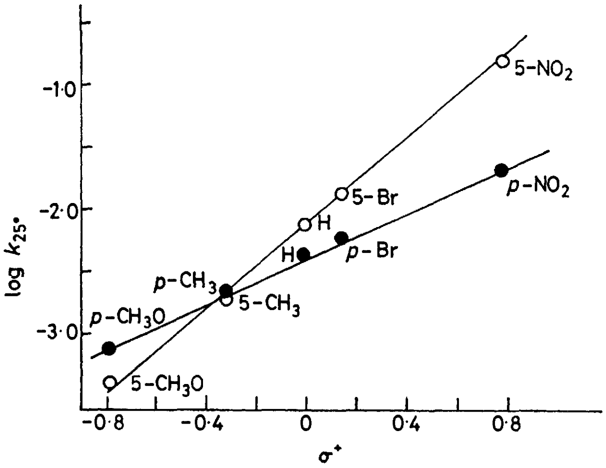

FIGURE 1 Plots of log $k_{25°}$ for the reactions of 5-substituted 2-furoyl chlorides (empty circles) and corresponding *para*-substituted benzoyl chlorides (full circles) with *m*-chloroaniline against σ^+ constants

The results show that the substituted 2-furoyl chlorides react with *m*-chloroaniline in benzene by the same mechanism as benzoylation involving attack of the lone pair electrons of the amino-group on the carbonyl carbon atom.[20] Correlation with σ^+ constants shows that the electron deficiency is conjugated with the substituent in the 5- or *para*-position and the electron-donating character of the heteroatom in the ground state is different from that in the transition state. The positive ρ value shows that the conjugation is less important in the transition state.[21]

These results are in agreement with a two-step S_AN mechanism,[22] where the rate-determining step is attack of the lone pair electrons of the amino-group on the carbonyl carbon atom. N–H bond-breaking cannot be rate determining in benzoylation, as proved by the observation of a kinetic isotope effect in the benzoylation of various deuterioanilines.[23]

By considering the heteroatom as a substituent replacing CH=CH in the benzene ring, 5-substituted 2-furoyl chlorides can be regarded as disubstituted benzene derivatives and therefore the substituent constant for the oxygen atom in the furan ring ($\sigma_{\alpha-0}$) can be calculated from equation (2) [24] assuming a constant ρ and

$$\log k = \rho(\sigma_X + \sigma_{\alpha-0}) + \log k_0 \qquad (2)$$

additivity of substituent effects. Inserting into equation (2) σ^+_X constants for the X substituents in the furan ring, ρ (0.91) and log k_0 (−2.386), the slope and the intercept of the plot of log k at 25° against σ^+ for the reaction of the benzoyl chlorides with *m*-chloroaniline, the $\sigma_{\alpha-0}$ value is a σ^+ constant, which we indicate as $\sigma^+_{\alpha-0}$. The $\sigma^+_{\alpha-0}$ values are −0.327 for 5-CH_3O, 0.063 for 5-CH_3, 0.280 for 5-H, 0.416 for 5-Br, and 0.949 for 5-NO_2. The substituent constants for the oxygen atom in the furan ring have been calculated previously. The $\sigma_{\alpha-0}$ constants were obtained from the pK_a of carboxylic acids,[10,25] the hydrolysis of carboxylic esters,[26] the solvolytic rearrangement of β-arylethyl tosylates,[27] and the pK_a of arenesulphonamides.[28] The $\sigma^+_{\alpha-0}$ constants were derived from solvolysis of 1-arylethyl acetates,[29] protiodemercuriation,[30] pyrolysis of 1-arylethyl acetates,[31] protiodesilylation,[32] electrophilic reactivity using the 'extended selectivity treatment,'[33] solvolysis of alkyl chlorides,[26] and from the reaction of arenesulphonyl chlorides with anilines.[34] The $\sigma^+_{\alpha-0}$ value calculated from these reactions is approximately constant. The $\sigma^+_{\alpha-0}$ value here reported is clearly variable indicating the possibility of proximity interactions between the heteroatom and the reaction centre and so altering the susceptibility of the side-chain to the influence of substituents.[10]

The rate constants for the reaction of 3-substituted 2-furoyl chlorides are faster than those for *ortho*-substituted benzoyl chloride reactions (Table 1). As observed in the reaction of 2-thenoyl chlorides with aniline [12] the methyl group retards and the bromine substituent accelerates the reaction. The reactivity of 3- and *ortho*-derivatives is faster than that of the 5- and *para*-analogues. The faster reaction rate of the 3- and *o*-methyl derivatives, by comparison with that of the 5- and *para*-substituted compounds is due to the smaller

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[19] F. L. Pilar and J. R. Morris, *J. Chem. Phys.*, 1961, **34**, 389.

[20] J. G. Mather and J. Shorter, *J. Chem. Soc.*, 1961, 4744.

[21] R. A. Jackson, 'Mechanism', Clarendon Press, Oxford, 1972, p. 110.

[22] E. M. Kosower, 'Introduction to Physical Chemistry', Wiley, New York, 1968, p. 65.

[23] J. J. Elliott and S. F. Mason, *Chem. and Ind.*, 1959, 488.

[24] C. D. Johnson, 'The Hammett Equation', Cambridge University Press, London and New York, 1973, p. 103.

[25] (*a*) F. Fringuelli, G. Marino, and A. Taticchi, *J.C.S. Perkin II*, 1974, 1738; (*b*) G. Marino, *Adv. Heterocyclic Chem.*, 1971, **13**, 242.

[26] G. T. Bruce, A. R. Cooksey, and K. Morgan, *J.C.S. Perkin II*, 1975, 551.

[27] D. S. Noyce and R. L. Castenson, *J. Amer. Chem. Soc.*, 1973, **95**, 1247.

[28] A. Ballistreri, E. Maccarone, G. Musumarra, and G. A. Tomaselli, *J.C.S. Perkin II*, 1977, 984.

[29] E. A. Hill, M. L. Gross, M. Stasiewicz, and M. Manion, *J. Amer. Chem. Soc.*, 1969, **91**, 7381.

[30] R. D. Brown, A. S. Buchanan, and A. A. Humffray, *Austral. J. Chem.*, 1965, **18**, 1513.

[31] R. Taylor, *J. Chem. Soc.* (*B*), 1968, 1397.

[32] R. Taylor, *J. Chem. Soc.* (*B*), 1970, 1364.

[33] S. Clementi, P. Linch, and G. Marino (*a*) *J. Chem. Soc.* (*B*), 1970, 1153; (*b*) *Tetrahedron Letters*, 1970, 1389; (*c*) G. Ciranni and S. Clementi, *ibid.*, 1971, 3833.

[34] E. Maccarone, G. Musumarra, and G. A. Tomaselli, *J.C.S. Perkin II*, 1976, 906.

conjugation between the negative charge on the reaction centre and the methyl group. The 3- and *o*-bromo-reactions are faster than those of the 5- and *para*-derivatives because the inductive effect of the bromine atom in the 3- and *ortho*-positions is greater than that in the 5- and *para*-position.[20]

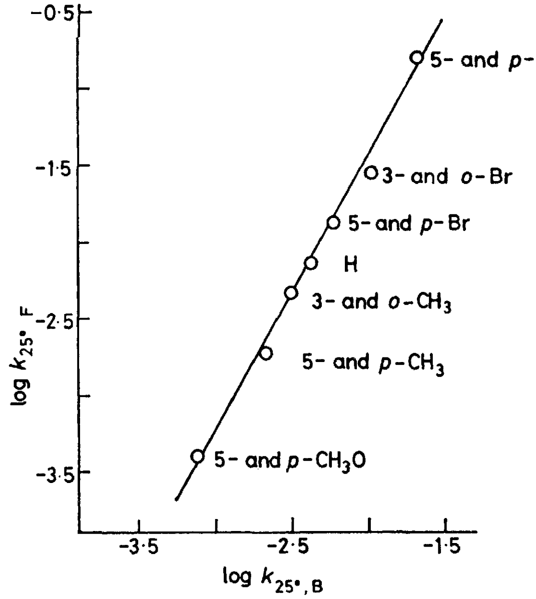

FIGURE 2 Plot of log $k_{25°}$ for the reactions of 3- and 5-substituted 2-furoyl chlorides with *m*-chloroaniline (F) against log $k_{25°}$ for the reactions of the corresponding *ortho*- and *para*-substituted benzoyl chlorides with *m*-chloroaniline (B)

A plot of log *k* at 25° for the reactions of 3- and 5-substituted 2-furoyl chlorides against log *k* at 25° for the reactions of the corresponding *ortho*- and *para*-substituted benzoyl chlorides is linear with a slope of 1.73 (r 0.989) (Figure 2). This value is similar to that calculated from the ratio $\rho : \rho' = 1.83$, where ρ is the reaction constant for reactions of 5-substituted 2-furoyl chlorides (1.67) and ρ' for those of *para*-substituted benzoyl chlorides (0.91). A value higher than unity with those for the reactions of 3- and 5-substituted 2-thenoyl chlorides and of corresponding *ortho*- and *para*-substituted benzoyl chlorides with aniline (1.27)[12] indicates that the furan ring is more efficient than benzene and thiophen in relaying the electronic effects of the substituents to the reaction centre. Also the points regarding the 3- and *ortho*-derivatives lie close to the line indicating that the same combination of factors is responsible for both the reactions of 5- and *para*-substituted and 3- and *ortho*-substituted acid chlorides, and that the substituent in the 3- and *ortho*-positions, compared with the unsubstituted compounds and the 5- and *para*-derivatives, in the transition state, compared with the initial state, does not exert restrictions on rotation of the aromatic ring relative to the carbonyl group.

EXPERIMENTAL

Materials.—3-Methyl-,[35] 5-methyl-,[36] 5-methoxy-,[37] and 3-bromo-2-furoic acids[38] were prepared as reported; 5-bromo- and 5-nitro-2-furoic acids were Aldrich products. The acid chlorides were prepared by treating the corresponding acids with thionyl chloride and purified by distillation or crystallization. 3-Methyl-2-furoyl chloride had m.p. 18.5—19.5° (from light petroleum);[39] 5-methyl-2-furoyl chloride, b.p. 91° at 30 mmHg;[36] 5-methoxy-2-furoyl chloride, b.p. 108° at 18 mmHg;[37] 3-bromo-2-furoyl chloride, m.p. 38—40° (from light petroleum);[40] 5-bromo-2-furoyl chloride, b.p. 24—26° at 0.2 mmHg;[41] 5-nitro-2-furoyl chloride, m.p. 38° (from chloroform).[42] *ortho*- and *para*-Substituted benzoyl chlorides (Aldrich) and *m*-chloroaniline (Carlo Erba) were distilled twice at reduced pressure. R. P. Carlo Erba benzene was used as solvent, no special purification being undertaken.[43]

Kinetic Measurements.—The reaction was followed kinetically, as previously,[12] by filtering the completely insoluble *m*-chloroaniline hydrochloride, dissolving it in water, and estimating the chloride with 0.01N-mercury(II) nitrate, using diphenylcarbazone as indicator, in the presence of Bromophenol Blue.

TABLE 2

Physical constants and analytical data of anilides[a]

X-2-*m*-Chloro-anilidofuran	M.p. (°C)		Analytical data (%)		
			C	H	N
H[b]	116				
3-CH$_3$	74	Found	61.4	4.2	5.8
		$C_{12}H_{10}ClNO_2$ requires	61.2	4.3	5.9
5-CH$_3$	100	Found	61.3	4.4	6.0
		$C_{12}H_{10}ClNO_2$ requires	61.2	4.3	5.9
5-CH$_3$O	122	Found	57.5	4.2	5.7
		$C_{12}H_{10}ClNO_3$ requires	57.3	4.0	5.6
3-Br	100	Found	44.3	2.4	4.9
		$C_{11}H_7BrClNO_2$ requires	44.0	2.3	4.7
5-Br	128	Found	44.2	2.4	4.8
		$C_{11}H_7BrClNO_2$ requires	44.0	2.3	4.7
5-NO$_2$	116	Found	49.7	2.7	10.6
		$C_{11}H_7ClN_2O_4$ requires	49.5	2.6	10.5
X C_6H_4-$CONHC_6H_4Cl$-*m*					
H[c]	124[c]				
o-CH$_3$	156[c]				
p-CH$_3$	119	Found	68.2	4.8	5.6
		$C_{14}H_{12}ClNO$ requires	68.4	4.9	5.7
p-CH$_3$O	134[c]				
o-Br	153	Found	50.5	3.8	4.7
		$C_{13}H_9BrClNO$ requires	50.3	2.9	4.5
p-Br	140	Found	50.4	2.8	4.7
		$C_{13}H_9BrClNO$ requires	50.3	2.9	4.5
p-NO$_2$	167[c]				

[a] All compounds were recrystallized from aqueous ethanol. [b] See ref. 14. [c] H. Schwartz and J. B. Skaptason, Belg.P 672,631 (1966) (*Chem. Abs.*, 1966, **65**, 15 282).

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[35] D. M. Burness, *Org. Synth.*, 1959, **39**, 46.

[36] A. L. Mndzhoyan, V. G. Afrikyan, and M. T. Grigoryan, *Doklady Akad. Nauk Armyan*, 1957, **24**, 207.

[37] D. G. Manly and E. D. Amstutz, *J. Org. Chem.*, 1956, **21**, 516.

[38] M. C. Zaluski, M. Robba, and M. Bonhomme, *Bull. Soc. chim. France*, 1970, 1838.

[39] E. Sherman and E. D. Amstutz, *J. Amer. Chem. Soc.*, 1950, **73**, 2195.

[40] D. J. Chadwich, J. Chambers, G. D. Meakins, and R. L. Snowden, *J.C.S. Perkin II*, 1976, 1.

[41] A. L. Mndzhoyan, *J. Gen. Chem.* (*U.S.S.R.*), 1946, **16**, 767.

[42] R. Marquis, *Compt. rend.*, 1903, **137**, 520.

[43] A. Arcoria, S. Fisichella, G. Scarlata, and D. Sciotto, *J. Org. Chem.*, 1973, **38**, 32.

The second-order rate constants were calculated for constant molar ratios of the reactants, acid chloride : *m*-chloroaniline 1 : 2, in agreement with equation (1). The initial concentration of the reactants after mixing were acid chloride 0.005M, *m*-chloroaniline 0.01M, acid chloride 0.0025M, and *m*-chloroaniline 0.005M for the 5-nitro-2-furoyl chloride reaction. All compounds gave excellent second-order kinetics. All rates were run in duplicate to at least 75—80% completion with <3% deviation between the two rate constants. All rate constants were calculated by a least-squares computer program with a Hewlett–Packard 9100 B instrument. The activation parameters were calculated from a least-squares treatment of log k against T^{-1}.

Products Analysis.—Standard solutions of the appropriate acid chloride (1 mol) and *m*-chloroaniline (2 mol) in benzene were placed in a glass-stoppered bottle and maintained at the kinetic temperature until completion. After concentration of the solution, the precipitated anilides (95% yield) were filtered, washed free from *m*-chloroaniline hydrochloride with water, dried, and recrystallized from aqueous ethanol. The physical constants and analytical data are reported in Table 2.

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