195°[12b]; m.p. 198°[11]); methyl ester by diazomethane esterification and crystallization from *n*-pentane at −40°, m.p. 34° (reported m.p. 33°[12b]).

Methyl 2,5-Dibromobenzoate (III).—The acid was prepared from 2,5-dibromotoluene by oxidation with nitric acid,[10] m.p. 151–152° (reported m.p. 153°[10]); amide, m.p. 182–183° (not reported); methyl ester (prepared as above), m.p. 40–41°.

Methyl 3,5-Dibromobenzoate (IV).—Prepared from anthranilic acid by the method of Bogert and Hand,[13] 3,5-dibromobenzoic acid melted at 217–218° (reported m.p. 219–220°[13]; m.p. 218.5–219.5°[8b]); amide, m.p. 185–186° (reported[10,12a] m.p. 187°); methyl ester, m.p. 51–52°.

Analysis of the Mixed Methyl Esters by Infrared Spectroscopy.—Treatment of the mixed dibromo acids with diazomethane without purification yielded an oil whose infrared spectrum was determined and compared with the spectra of the pure esters (Table I). Quantitative comparison could not be expected to give excellent results because the mixture of methyl esters contains at least one unidentified substance in addition to II and III. In Table II the results of estimating the relative amounts of II and III are shown using six appropriate bands. There is 33.5 ± 8% of II and 66.5 ± 8% of III neglecting the impurities. By way of confirmation the spectrum of a mixture of II and III (34/66) agreed better with the unknown than 30/70 or 40/60 synthetic mixtures.

TABLE II

Cm.$^{-1}$	II, %	III, %
1575	46	
1384	[27]	73
1367	36	
970	[20]	80
875	37	
827	35	

KATONAH, NEW YORK

---

(12) (a) J. J. Sudborough, *J. Chem. Soc.*, 587 (1895); (b) *ibid.*, 601 (1895).

(13) M. T. Bogert and W. F. Hand, THIS JOURNAL, **25**, 935 (1903).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

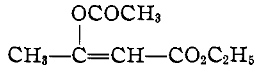
Mechanism of the O-Benzoylation of Ethyl Benzoylacetate in Pyridine

BY WILLIAM R. GILKERSON,[1] WILLIAM J. ARGERSINGER, JR., AND WILLIAM E. MCEWEN

RECEIVED AUGUST 3, 1953

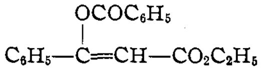
The rate of formation of ethyl β-benzoxycinnamate (II) from benzoyl chloride and ethyl benzoylacetate in pyridine solution at 25° has been measured. The rate data are best interpreted as indicating an initial condensation reaction between the benzoylpyridinium cation (VIII) and the enol form of ethyl benzoylacetate to give both ethyl benzoyl-(1-benzoyl-1,4-dihydro-4-pyridyl)-acetate (XA) and ethyl benzoyl-(1-benzoyl-1,2-dihydro-2-pyridyl)-acetate (XIA). The latter rearranges *via* a quasi six-membered ring transition to give pyridine and ethyl β-benzoxycinnamate (II).

The present study was undertaken in an effort to determine the mechanism of the reaction of an acid chloride with a β-ketoester in pyridine solution. This reaction represents a well known synthetic method for the preparation of the O-acyl derivative. Examples include the preparation of ethyl O-acetylacetoacetate (I) from ethyl acetoacetate and acetyl chloride,[2] and of ethyl β-benzoxycinnamate (II) from ethyl benzoylacetate and benzoyl chloride.[3,4] The yields of the O-acyl derivatives, I and II, are excellent, and there is no evidence that either of the isomeric C-acyl derivatives, ethyl diacetylacetate (III) and ethyl dibenzoylacetate (IV), respectively, is formed in the reaction.



$CH_3—\overset{OCOCH_3}{C}=CH—CO_2C_2H_5$

I



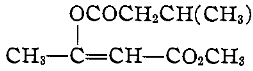
$C_6H_5—\overset{OCOC_6H_5}{C}=CH—CO_2C_2H_5$

II

$(CH_3CO)_2CHCO_2C_2H_5$ III

$(C_6H_5CO)_2CHCO_2C_2H_5$ IV

The situation with respect to the use of other tertiary amines as the solvent is somewhat confused. Claisen and Haase[5] reported that the use of dimethylaniline and antipyrine led to the formation of O-acyl derivatives, but they gave no experimental details. Bouveault and Bongert[6] prepared methyl O-isovalerylacetoacetate (V) in 55% yield by the reaction of isovaleryl chloride with methyl acetoacetate in diethylaniline, but they did not indicate whether any of the C-acyl derivative also was formed. They did make a qualitative statement, however, to the effect that the conversion to the O-acyl derivative is more nearly complete in pyridine solution than in diethylaniline.



$CH_3—\overset{OCOCH_2CH(CH_3)_2}{C}=CH—CO_2CH_3$

V

The main result of the reaction of the sodium salt of a β-ketoester with an acid chloride in an inert solvent is C-acylation. Small amounts of the O-acyl derivatives are sometimes isolated in these reactions.[7–11] The observation by Claisen and Haase[8] that ethyl O-acetylacetoacetate (I) was isomerized to ethyl diacetylacetate (II) by the action of the sodium salt of ethyl acetoacetate led these workers to suggest that the O-acyl derivative is an intermediate in the formation of the C-acyl derivative. This suggestion has been refuted by Dieckmann and Stein[12] and also by Michael and Carlson,[11] who demonstrated that the reaction of the sodium salt of a β-ketoester with an acid chloride can give the C-acyl derivative under conditions which do not permit the isomerization of the O-acyl derivative to the C-acyl derivative. In other words, they

---

(1) Atomic Energy Commission Fellow, 1951–1953.

(2) L. Claisen and E. Haase, *Ber.*, **33**, 1242 (1900).

(3) L. Claisen, *Ann.*, **297**, 2 (note) (1897).

(4) S. M. McElvain and D. Kundiger, THIS JOURNAL, **64**, 254 (1942).

(5) L. Claisen and E. Haase, *Ber.*, **36**, 3674 (1903).

(6) L. Bouveault and A. Bongert, *Bull. soc. chim.*, [3] **27**, 1160 (1902).

(7) L. Claisen and W. Zedel, *Ann.*, **277**, 164 (1893).

(8) L. Claisen and E. Haase, *Ber.*, **33**, 3778 (1900).

(9) L. Bouveault and A. Bongert, *Bull. soc. chim.*, [3] **27**, 1038 (1902).

(10) A. Michael, *Ber.*, **38**, 2083 (1905).

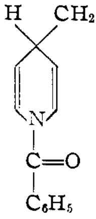
(11) A. Michael and G. H. Carlson, THIS JOURNAL, **57**, 165 (1935).

(12) W. Dieckmann and R. Stein, *Ber.*, **37**, 3392 (1904).

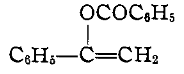
have demonstrated that the rate of isomerization of the O-acyl derivative to the C-acyl derivative is slower than the rate of direct C-acylation.

It would be desirable that a mechanism for the reaction in pyridine embody an explanation of the apparently exclusive formation of the O-acyl derivative. There is recent evidence available[13] to show that the use of other tertiary amines, quinoline and dimethylaniline, leads to the formation of a high proportion of the C-acyl derivative. Therefore the following discussion will be restricted to reactions carried out in pyridine solution.

A mechanism for O-acylation which is strongly dependent on the solvent, pyridine, has recently been proposed.[14] It was found that reaction of pyridine, acetophenone and benzoyl chloride at room temperature for several months afforded 1-benzoyl-4-phenacyl-1,4-dihydropyridine (VI) and O-benzoylacetophenone (VII) as two of the products. It was also demonstrated that under comparable conditions VI was not an intermediate in the formation of VII, nor was VII an intermediate in the formation of VI. It was hypothesized that VI arose from condensation of the benzoylpyridinium cation (VIII), electron deficient in the α- and γ-positions, with the electron-donating enolic tautomer of acetophenone. Presumably condensation also occurred at the α-position to give 1-benzoyl-2-phenacyl-1,2-dihydropyridine, but the failure to isolate this substance was attributed to its relatively rapid rearrangement *via* a quasi six-membered ring transition (IX) to give pyridine and O-benzoylacetophenone (VII).

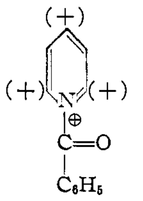


VI

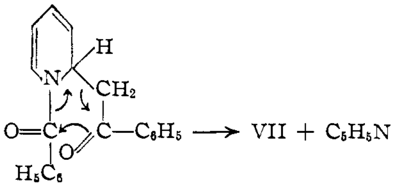


$$C_6H_5-\overset{\displaystyle OCOC_6H_5}{C}=CH_2$$

VII

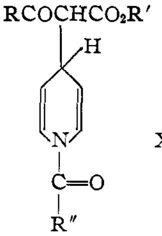


VIII

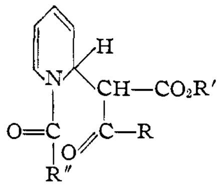


IX

With β-ketoesters it was proposed[14] that the initial reaction still involves carbon–carbon bond formation at the α- and γ-positions of the acylpyridinium salt to give X and XI and that the enhanced acidity of the β-ketoesters makes the interconversion of X and XI relatively rapid. The product is, therefore, the O-acyl derivative of the β-ketoester, derived exclusively from the condensation product, XI.



X
XA R = R'' = C_6H_5
R' = C_2H_5



XI
XIA R = R'' = C_6H_5
R' = C_2H_5

Another tertiary amine, such as dimethylaniline, could not participate in such a mechanism, since a condensation product analogous to XI could not be formed. On superficial consideration it might be assumed that quinoline would give the same type of reactions as pyridine. Yet our experiences have led us to the conclusion that the differences between the systems benzoyl chloride–pyridine and benzoyl chloride–quinoline are far more numerous than the similarities. Several examples can be cited. Reaction of pyridine, benzoyl chloride and dimethylaniline affords 4-*p*-dimethylaminophenylpyridine plus benzaldehyde, while the corresponding reaction in quinoline yields 1-benzoyl-2-*p*-dimethylaminophenyl-1,2-dihydroquinoline.[15,16] Reaction of pyridine, benzoyl chloride and nitromethane gives mainly N,N′-dibenzoylurea, whereas reaction in quinoline gives a red product, $C_{27}H_{19}N_3O$.[17] Reaction of benzoyl chloride, ethyl benzoylacetate and quinoline yields considerable ethyl dibenzoylacetate (IV)[13] in contrast to the apparently exclusive formation of ethyl β-benzoxycinnamate (II) in pyridine.[4,14] Reaction of acetophenone, benzoyl chloride and quinoline affords no O-benzoylacetophenone (VII), but 1-benzoyl-2-phenacyl-1,2-dihydroquinoline can be isolated.[13] The latter product shows no tendency to rearrange to give VII and quinoline. Benzoyl chloride and ethyl cyanoacetate also react to give markedly different types of condensation products in pyridine and quinoline.[17]

It was felt that an investigation of the kinetics of the reaction of a β-ketoester with an acid chloride in pyridine would clarify some aspects of the mechanism. The combination of ethyl benzoylacetate and benzoyl chloride was chosen because of the ease of purification of starting materials and products, the essential completeness of reaction, the lack of side reactions and the analogy with other reactions studied in these laboratories and elsewhere.

A severe limitation on the range of concentrations available for kinetic studies at 25° became apparent shortly after the work was commenced. In the first place, the reaction is so fast that an upper limit on the concentrations must be set. For example, when the initial concentrations of both ester and acid chloride are greater than 0.05 *M*, the reaction is almost 50% complete before the first measurement can be made (110 seconds). In the second place,

---

[13] Paul E. Wright and W. E. McEwen, unpublished work.

[14] W. von E. Doering and W. E. McEwen, THIS JOURNAL, **73**, 2104 (1951).

[15] E. Koenigs and E. Ruppelt, *Ann.*, **509**, 142 (1934).

[16] W. E. McEwen, R. H. Terss and I. W. Elliott, THIS JOURNAL, **74**, 3605 (1952).

[17] R. H. Terss and W. E. McEwen, unpublished work.

despite extreme care to exclude moisture from the reaction system, there was always a residual water concentration of about 0.01 *M*. This water reacts very fast with pyridine and benzoyl chloride to form pyridinium chloride (pyridine hydrochloride) and probably pyridinium benzoate. Adkins and Thompson[18] have described a procedure for the preparation of acid anhydrides by treating anhydrous acylpyridinium salts with an equivalent of water at a low temperature. The presence of water in the pyridine at the time of formation of the acylpyridinium salt lowers the yield of acid anhydride. This implies that water already present in pyridine at the time of addition of the benzoyl chloride brings about formation of pyridinium chloride and pyridinium benzoate. In any event, titration of a benzoyl chloride–pyridine solution, after it had been mixed with water, required exactly two moles of sodium hydroxide per mole of benzoyl chloride. If any benzoic anhydride is formed, it is quantitatively hydrolyzed in the titration procedure. In order to have benzoyl chloride available for reaction with ethyl benzoylacetate, then, it was necessary for its concentration to be greater than 0.01 *M*. The practical concentration range of benzoyl chloride available for the kinetic study was therefore restricted to 0.01–0.05 *M*.

Since the method of analysis employed to follow the rate of reaction involved quenching of the reaction mixture in water, followed by titration of the mixed acids with standard sodium hydroxide solution, and since there was always some pyridinium chloride and pyridinium benzoate present at the start of the reaction resulting from the inevitable moisture present in the system, it was necessary to employ a greater concentration of ethyl benzoylacetate than benzoyl chloride in the various runs. Then the effective initial concentrations of benzoyl chloride (a_0) could be calculated as the amount of benzoyl chloride which was consumed in reaction with ethyl benzoylacetate to form II during a period of 24 hours, a period of time more than adequate for complete reaction. The initial concentration of pyridinium chloride (x_0) could, in turn, be calculated from the difference between the total amount of benzoyl chloride originally added to the pyridine (concentration = a) and that which reacted with the ester in a complete reaction.

The order of the reaction with respect to the concentrations of species present initially was determined from the variation of the initial instantaneous rates of reaction (S_0) with concentration. Table I lists the various initial concentrations of reagents, the initial rates of reaction (S_0) and the following three sets of proposed rate constants: $k_1 = S_0/a_0b$; $k_2 = S_0x_0/a_0b$; $k_3 = S_0x_0^{1/2}/a_0b$. The symbols S_0, x_0 and a_0 have the meanings described above, and b is the initial concentration of ethyl benzoylacetate.

TABLE I

ORDER OF REACTION WITH RESPECT TO INITIAL CONCENTRATIONS

p, 0.005 mole per liter of pyridinium chloride added; q, includes the added pyridinium chloride; r, 0.0317 mole per liter of pyridinium chloride added.

Expt.	$a_0 \times 10^2$, moles/l.	$b \times 10^2$, moles/l.	$x_0 \times 10^2$, moles/l.	$S_0 \times 10^5$, moles/l.-sec.	$k_1 \times 10^2$, l./mole-sec.	$k_2 \times 10^4$, sec.$^{-1}$	$k_3 \times 10^3$, l.$^{1/2}$/mole$^{1/2}$-sec.
1	0.374	1.77	0.869	0.461	6.97	6.05	6.50
2	0.493	3.38	.766	1.15	6.90	5.29	6.04
3	1.137	3.52	.749	2.79	6.95	5.20	6.01
4	3.07	4.26	1.41	6.82	5.21	7.35	6.19
5	1.87	5.12	0.646	8.23	8.59	5.55	6.90
6	2.27	2.93	1.14	3.98	5.98	6.82	6.38
7	2.77	6.57	1.23	10.8	5.94	7.30	6.59
8^p	2.69	4.59	1.29^q	7.10	5.75	7.42	6.52
9^r	2.89	5.85	4.64^q	4.85	2.87	13.3	6.18

It is clear from Table I that the second-order rate expression corresponding to k_1 can be rejected inasmuch as k_1 varies from 2.87×10^{-2} to 8.59×10^{-2}. The rate expression corresponding to k_2 can also be rejected, particularly as a result of experiment 9, when excess pyridinium chloride was added to the reaction mixture. The rate expression corresponding to k_3 appears to be the correct one for the initial reaction since $k_3 = 6.37 \times 10^{-3} \pm 2\%$ for the nine experiments.

Since the concentration of pyridinium chloride appears to the half power in the expression for k_3, it is clear that there is inhibition either by chloride ion or pyridinium ion. The data of Table II show that the inhibition is caused by chloride ion.

TABLE II

INITIAL RATES WITH PYRIDINIUM NITRATE AND LITHIUM CHLORIDE PRESENT

p, the solution was 0.0534 *M* in lithium chloride; q, the solution was 0.00033 *M* in pyridinium nitrate; r, the solution was 0.0364 *M* in pyridinium nitrate.

Exp.	$a_0 \times 10^2$ moles/l.	$b \times 10^2$ moles/l.	$x_0 \times 10^2$ moles/l.	$S_0 \times 10^5$ moles/l.-sec.	$k_3 \times 10^3$ l.$^{1/2}$/mole$^{1/2}$-sec.
10^p	1.80	4.39	1.14	0.730	0.986
11^q	2.04	4.32	1.35	3.99	5.25
12^r	1.99	5.03	1.20	5.72	6.25

Thus the kinetic expression for the initial reaction may be given by equation 1.

$$S_0 = k_3(C_6H_5COCl)(C_6H_5COCH_2CO_2C_2H_5)/(Cl^-) \quad (1)$$

There is ample evidence that benzoyl chloride reacts with pyridine to give at least an equilibrium concentration of benzoylpyridinium chloride (XII).[18-21] This exists in pyridine mainly in the form of ion pairs, there being only a small equilibrium concentration of free benzoylpyridinium ion (VIII) and chloride ion.[21,22]

$$C_6H_5COCl + C_5H_5N \underset{}{\overset{K_1}{\rightleftharpoons}} (C_6H_5CO\text{—}\overset{+}{N}C_5H_5,\ Cl^-) \overset{K_2}{\rightleftharpoons} VIII + Cl^-$$

The concentration of free benzoylpyridinium ion (VIII) is then given by equation 2.

$$(VIII) = \frac{K_1K_2(C_6H_5COCl)(C_5H_5N)}{(Cl^-)} = \frac{K'(C_6H_5COCl)}{(Cl^-)} \quad (2)$$

The concentration of the enol form of ethyl benzoylacetate in pyridine at 25° is not known, but the data of Meyer and Wilson[23] permit the generalization that increasing solvent basicity and increas-

---

(18) H. Adkins and Q. Thompson, THIS JOURNAL, **71**, 2242 (1949).

(19) V. Prey, *Ber.*, **75**, 537 (1942).

(20) W. M. Dehn and A. A. Ball, THIS JOURNAL, **36**, 2091 (1914).

(21) M. M. Davies, *Trans. Faraday Soc.*, **31**, 1561 (1935).

(22) D. S. Burgess and C. A. Kraus, THIS JOURNAL, **70**, 706 (1948).

(23) K. H. Meyer and F. G. Wilson, *Ber.*, **47**, 832 (1914). *Cf.* A. E. Remick, "Electronic Interpretations of Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1949, p. 453.

ing solvent polarity decrease the concentration of the enol form. Pyridine is more basic than water, but it has a lower dielectric constant than water. One may then make the crude estimate that these effects balance one another and that the ratio (enol)/(keto) in pyridine is of the same order of magnitude as in water, about 0.01. The concentration of the enol form of ethyl benzoylacetate may therefore be expressed by equation 3, K_3 being the equilibrium constant for the keto–enol equilibrium. The enol form of ethyl benzoylacetate will be designated hereafter as XIII.

$$(\text{XIII}) = K_3(\text{keto form}) \cong K_3(\text{C}_6\text{H}_5\text{COCH}_2\text{CO}_2\text{C}_2\text{H}_5) \quad (3)$$

From equations 1, 2 and 3, the new rate expression 4 may be written.

$$S = k'(\text{VIII})(\text{XIII}) \quad (4)$$

By analogy, equation 4 is in agreement with the mechanism originally proposed[14] for the formation of 1-benzoyl-4-phenacyl-1,4-dihydropyridine (VI) and O-benzoylacetophenone (VII) from pyridine, benzoyl chloride and acetophenone. The tremendous difference in the speeds of the reactions involving acetophenone on the one hand, and ethyl benzoylacetate on the other hand, may also be understood in terms of equation 4. The concentration of the enol form of acetophenone would be smaller than the concentration of the enol form of ethyl benzoylacetate by a factor of several powers of ten, and the rates of the two reactions would also differ accordingly.

The determination of the order of the O-acylation reaction with respect to time, *i.e.*, within the runs, shows a marked divergence from the order of the initial reaction. Table III lists the instantaneous rates of reaction ($S = dx/dt$) at times t, and the rate constants (k_4) based on an expression analogous to that found to hold for the initial reaction and shown in equation 5. The concentrations of ethyl β-benzoxycinnamate (II) at times t are given by x. The variation of k_4 within the runs is quite marked, especially when the pyridinium chloride concentration is low.

$$k_4 = S(x_0 + x)^{1/2}/(a_0 - x)(b - x) \quad (5)$$

Empirically, however, it was found that the concentration dependence of the rate within an experiment fitted equation 6, with the symbols of equation 6 being defined by equations 7 and 8.

$$S = k_5(C_0 - x) \quad (6)$$

$$k_5 = k_6 b/x_0^{1/2} \quad (7)$$

$$C_0 = K_4 a_0 \quad (8)$$

The values of C_0 and the various constants found in equations 6, 7 and 8 are given in Table IV. These values were obtained by drawing the best straight line (see Fig. 1) through the second, third and fourth points in a plot of S *vs.* x, the values of S corresponding to those found in Table III, and the values of x (also listed in Table III) at the various times t read from a plot of x *vs.* t. The first point (at an early time) was ignored in each case because it was felt that the benzoyl chloride might not yet have reacted completely with the water present in the system. As may be seen in Fig. 1, it was actually found that the first point did not fall on the straight line defined by the other three points.

TABLE III

ORDER OF REACTION WITH RESPECT TO TIME

Expt.	t, sec.	$S \times 10^5$, moles/l.-sec.	$x \times 10^2$, moles/l.	$k_4 \times 10^3$, l.$^{1/2}$/mole$^{1/2}$-sec.
1	250	0.257	0.083	5.09
	500	.143	.137	3.69
	750	.110	.169	3.40
	1000	.0821	.193	2.95
2	100	.745	.133	6.04
	200	.468	.191	4.75
	300	.339	.232	4.11
	400	.267	.262	3.76
3	100	1.67	.20	5.68
	200	1.07	.35	4.80
	300	0.800	.46	4.43
	400	0.625	.55	4.10
4	125	3.25	.75	5.86
	250	1.99	1.09	5.00
	375	1.48	1.32	5.22
	500	1.17	1.49	4.56
5	100	2.63	0.527	4.62
	200	1.45	.733	3.41
	300	0.998	.860	2.85
	400	0.727	.945	2.37
6	200	1.83	.557	5.85
	300	1.41	.718	5.58
	400	1.14	.846	5.42
	500	0.947	.952	5.23
7	200	3.38	1.25	6.55
	300	2.20	1.53	5.82
	400	1.59	1.72	5.34
	500	1.25	1.86	5.10
8	100	3.66	0.57	5.86
	200	2.36	0.87	5.12
	300	1.72	1.07	4.64
	400	1.41	1.22	4.51
9	100	3.38	0.40	5.59
	200	2.74	.72	5.69
	300	2.14	.97	5.40
	400	1.73	1.16	5.13
10	100	0.586	0.070	0.878
	200	0.411	.120	.657
	300	0.323	.157	.541
	400	0.290	.188	.504
11	100	2.70	.32	5.07
	200	1.92	.55	4.71
	300	1.45	.72	4.39
	400	1.13	.86	4.12
12	100	2.56	.40	4.40
	200	1.80	.62	4.02
	300	1.40	.78	3.83
	400	1.17	.92	3.87

TABLE IV

EMPIRICAL DEPENDENCE OF RATE ON CONCENTRATION

Expt.	$k_5 \times 10^3$	$C_0 \times 10^2$	K_4	$k_6 \times 10^3$
1	1.33	0.22	0.64	7.02
2	2.91	.35	.75	7.52
3	2.65	.79	.69	6.52
4	2.19	2.01	.66	6.09
5	3.43	1.16	.62	5.38
6	1.92	1.37	.65	6.99
7	3.19	2.23	.59	5.38
8	2.32	1.84	.68	5.73
9	2.07	1.99	.69	7.60
		Av.	.66	6.47 ± 11%

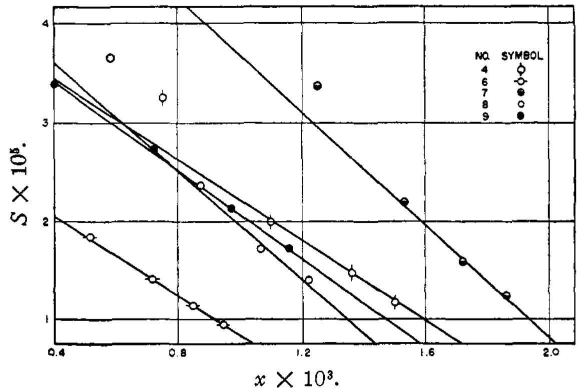


Fig. 1.—Plots of instantaneous rates of reaction (S = dx/dt) at times t *vs.* the concentrations (x) of ethyl β-benzoxycinnamate at times t. Similar plots for the runs not shown in this figure can be constructed from the data of Table III.

The form of the empirical rate equation 6, including the dependence of C_0 upon the initial concentration of benzoyl chloride, rules out the possibility of a rate-determining enolization of ethyl benzoylacetate. The possibility that the formation of free benzoylpyridinium ion (VIII) is the rate-determining step is also unlikely since the rate within a run would then depend on the total concentration of benzoyl chloride and not on just a fraction of that concentration.

The form of the rate equation within a run suggests that a portion of the benzoylpyridinium chloride forms a relatively unreactive complex other than that with chloride ion very early in the reaction. The previously proposed mechanism[14] involves just such a complex in the 1,4-addition product X. The reactions occurring are summarized in equation 9.

$$C_5H_5\overset{+}{N}H + XA \underset{k_{-7}}{\overset{k_7}{\rightleftarrows}} VIII + XIII \underset{k_{-8}}{\overset{k_8}{\rightleftarrows}} \underset{C_5H_5\overset{+}{N}H^+}{XIA} \xrightarrow{k_9} II \qquad (9)$$

On the basis of electronic theory, it might be anticipated that XIII would condense with equal facility at either of the two α-positions and at the γ-position of VIII. On a statistical basis, then, the rate of formation of XIA would be twice as great as that of XA. In this connection it is significant that $K_4 = 0.66$ (see Table IV).

On the basis of the analogy with the reaction of benzoyl chloride, acetophenone and pyridine to give 1-benzoyl-4-phenacyl-1,4-dihydropyridine (VI) and O-benzoylacetophenone (VII), and on the basis of the fact that VI, in a separate experiment, gave no isolable quantity of VII in contact with pyridinium chloride and pyridine during an equal length of time,[14] it may be assumed that $k_7 >> k_{-7}$. Since the conversion of XIA to II represents an intramolecular process involving a geometrically favorable quasi six-membered ring transition, it may be assumed that $k_9 >> k_8$.

These considerations, together with the conclusions expressed in equations 2 and 3, indicate that only a fraction ($K_4a_0 \cong {}^2/_3a_0$) of the benzoyl chloride is potentially available for formation of II in the early stages of the reaction. Thus the rate expression for relatively early reaction to produce II may be given as shown in equation 10.

$$S = \frac{k(K_4a_0 - x)(b - [1 - K_4]a_0 - x)}{(x_0 + x)^{1/2}} \qquad (10)$$

Since $K_4 > 1 - K_4$, $x_0 > x$ and $b > a_0$ in the early part of all the kinetic runs described in this paper, the rate expression may be approximated as shown in equation 11, which has the form of the empirically determined equation 6.

$$S = kb(K_4a_0 - x)/x_0^{1/2} \qquad (11)$$

The addition of a relatively large quantity of lithium chloride to the reaction mixture brought about a significant change in the apparent order of reaction within the run, as may be seen in Fig. 2. Although the dissociation constant of lithium chloride in pyridine at 25° is not known, its order of magnitude relative to that of pyridinium chloride may be estimated. A number of strong electrolytes, such as sodium iodide, have dissociation constants about ten times greater than that of pyridinium nitrate ($K = 5.1 \times 10^{-5}$).[21] The dissociation constant of pyridinium chloride has been determined[23a] to be $K = 1.4 \times 10^{-5}$. Thus, as a first approximation, the dissociation constant of lithium chloride may be taken as about 10–30 times that of pyridinium chloride.

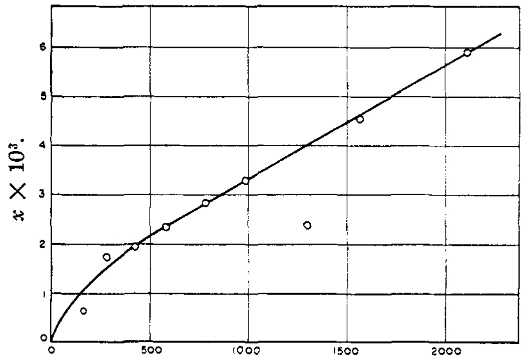


Fig. 2.—Plot of concentration (x) of ethyl β-benzoxycinnamate *vs.* time for experiment 10, in which an excess of lithium chloride was added to the reaction mixture.

In experiment 10 (Fig. 2), where the chloride ion concentration was much greater than in any other run, the order of reaction became zero after about 400 seconds. It has been shown from the initial rate data that the effect of increasing the chloride ion concentration is to decrease the concentration of free benzoylpyridinium ion (VIII). It is presumed, however, that the rates of formation and dissociation of benzoylpyridinium chloride are greater than those for the other processes occurring in the reaction mixture.[24]

The data for experiment 10 (Fig. 2) indicate that equation 12 holds after about 400 seconds.

$$S = \mathrm{d}x/\mathrm{d}t = \text{a constant} \qquad (12)$$

This would imply that, after 400 seconds,

[23a] W. R. Gilkerson, C. A. Reynolds, W. J. Argersinger and W. E. McEwen, unpublished work.

[24] H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, N. Y., 1950, p. 66.

(VIII)(XIII) = a constant. Then the relationship shown in equation 13 would also be valid.

$$\text{(VIII)d(XIII)}/dt + \text{(XIII)d(VIII)}/dt = 0 \quad (13)$$

The only way in which the relationship expressed in equation 13 could be true would be for some reversible reaction to be in operation, a reaction which reduces the concentrations of both VIII and XIII to a steady value. The reversible formation of XA and pyridinium ion from VIII and XIII (equation 9) accounts for the observed behavior.

Experimental

Materials.—J. T. Baker C.P. pyridine was refluxed over anhydrous potassium hydroxide for 24 hours and then distilled. The distillate was refluxed over anhydrous barium oxide, in a dry nitrogen atmosphere, for 48 hours. The pyridine was then fractionated through a 90-cm. packed column at atmospheric pressure. The fraction boiling within ±0.1° of the correct b.p. at the prevailing pressure was collected. Atmospheric moisture was excluded from the system during the various operations.

J. T. Baker C.P. benzoyl chloride was distilled at 6–7 mm. pressure, material of b.p. 73° being collected.

Ethyl benzoylacetate (Eastman Kodak Co. red label) was distilled at 6 mm. pressure, the fraction of b.p. 142–143° being collected.

Pyridinium chloride was prepared by passing anhydrous hydrogen chloride into a benzene solution of pyridine. The crude product was crystallized from absolute ethanol and dried in a vacuum desiccator over phosphorus pentoxide.

Anal. Calcd. for $C_5H_5N{\cdot}HCl$: Cl, 30.67. Found: Cl, 30.48, 30.67.

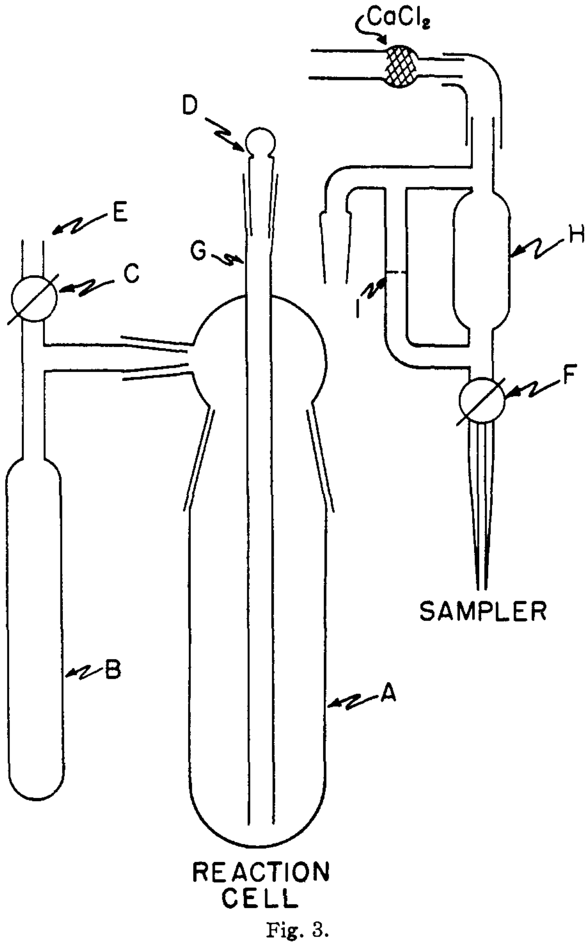


Fig. 3.

Pyridinium nitrate was prepared by the method of Pincussohn.[25] The salt was twice recrystallized from absolute ethanol and dried in a vacuum desiccator over phosphorus pentoxide.

Anal. Calcd. for $C_5H_5N{\cdot}HNO_3$: neut. equiv., 142.1. Found: neut. equiv., 141.4, 141.7.

Lithium chloride (J. T. Baker analyzed) was dried over phosphorus pentoxide in a vacuum desiccator.

Analysis of Benzoyl Chloride in Pyridine Solution.—The transfer of benzoyl chloride, in a weighing buret, to the flask containing pyridine was carried out in a dry-box under an atmosphere of dried nitrogen. The method of analysis adopted for benzoyl chloride in pyridine solution was based on the procedure of Smith and Bryant.[26] A 5.000-ml. aliquot of the solution was pipetted into 10.0 ml. of water and then titrated to the phenolphthalein end-point with standard sodium hydroxide solution. All titrations were carried out using a 5-ml. microburet, graduated in 0.01-ml. divisions. That the method is suitable may be seen from Table V. The percentage deviation was ±0.5%.

Table V

Titration of 5.000 Ml. of 0.01114 *M* Benzoyl Chloride in Pyridine with 0.01007 *M* Sodium Hydroxide Solution

Sample	Base, ml.	*N* (observed)
1	11.104	0.02235
2	11.108	.02236
3	11.012	.02215
4[a]	11.140	.02244

[a] Some ethyl β-benzoxycinnamate was added to the solution.

Titration of Ethyl Benzoylacetate in Pyridine Solution.—In the course of the experiments it was found that ethyl benzoylacetate in a pyridine–water solution was acidic enough to require a measurable quantity of sodium hydroxide solution to be neutralized to the phenolphthalein end-point. By keeping the pyridine–water ratio approximately constant, the amount of base required could be simply related to the concentration of the ester. The solutions were prepared and the titrations carried out as described above for benzoyl chloride in pyridine. Titration of a series of nine solutions established that the apparent normality (N) of the ethyl benzoylacetate could be correlated with the concentration of the ester (b) by means of the relationship

$$K = N/(b - N) = 0.0905 \pm 8\%$$

In the actual kinetic runs (see below) the part of the observed normality due to unreacted ethyl benzoylacetate was calculated by use of an apparent fraction of ethyl benzoylacetate ionized

$$\alpha = N/b = K/(1 + K) = 0.083$$

Rates of Reaction of Benzoyl Chloride with Ethyl Benzoylacetate in Pyridine at 25°.—All pieces of glassware used in the following runs were rinsed with distilled water and dried in a vacuum oven. Solutions (approximately 100 and 50 g., respectively) of benzoyl chloride and ethyl benzoylacetate in pyridine were prepared separately in 100-ml. glass-stoppered volumetric flasks, in a dry-box. Approximately 70 g. of the benzoyl chloride solution was transferred to flask A of the reaction cell (Fig. 3). About 20 g. of the ester solution was placed in the side-arm B (Fig. 3). Dow–Corning high-vacuum glass lubricant was used on the standard taper joints to obtain moisture-proof seals and to lessen the chance of the reaction cell coming apart during a run. Rubber bands provided a mechanical fastening for the various parts. The cell, with the stop-cock C closed, and the stopper D in place, was then removed from the dry-box and placed in a well stirred water-bath. The relative positions shown in Fig. 3 were maintained throughout this operation. The bath temperature was kept at 25.00 ± 0.025°, as determined with a Beckmann thermometer which had been checked against an Anschütz thermometer calibrated by the National Bureau of Standards. At least one hour was allowed for the solution to come to temperature equilibrium.

---

[25] L. Pincussohn, *Z. anorg. Chem.*, **14**, 385 (1897).

[26] D. M. Smith and W. M. D. Bryant, This Journal, **57**, 61 (1935).

During this time, the flasks with the remaining benzoyl chloride and ester solutions were weighed to determine the amounts transferred to the cell. The final concentrations of reactants were calculated in the following manner

wt. of C_6H_5COCl in the cell = wt. of C_6H_5COCl in flask originally × wt. of solution added to cell/original wt. of solution

wt. of pyridine added with the C_6H_5COCl = wt. of C_6H_5COCl solution added − wt. C_6H_5COCl added

The molar concentration of C_6H_5COCl in cell after mixing = wt. C_6H_5COCl in the cell × density of pyridine (at 25°) × 1000/molecular wt. of C_6H_5COCl × total wt. of pyridine in the cell

The total weight of pyridine in the cell includes that added with the ester. The concentration of ethyl benzoylacetate was determined similarly. In calculating the molar concentration, it was assumed that the densities of the benzoyl chloride and ester solutions were approximately the same as that of pure pyridine. The density of the latter was taken as 0.978 at 25°.[27] After the solutions in the cell had reached bath temperature, the cell was removed from the bath. The side-arm B was tilted, allowing the ester solution to flow into flask A, where it was thoroughly mixed with the benzoyl chloride solution. Timing of the reaction began at the mid-point of the mixing process. The latter was finished as quickly as possible (10–15 sec.) so that the cell could be replaced in the bath. A one-way syringe was then attached to tube E by a short piece of rubber tubing. The stopper D was removed and the sampler fitted to the cell at the same point.

In taking a sample, stop-cock C was opened, and the solution in A was pushed by means of the syringe up tube G. Compartment H was filled until the liquid level reached the mark I, placed so that about 7 ml. of solution would be delivered. The stop-cock F, otherwise kept closed, was then opened, draining the solution into a dry 25-ml. erlenmeyer flask. A 5.000-ml. sample of this solution was then pipetted into 10.0 ml. of water, shaken thoroughly and allowed to stand for several minutes. The water solution was titrated to the phenolphthalein end-point with sodium hydroxide solution which had been standardized against 5.000-ml. portions of the original benzoyl chloride–pyridine solution in 10.0 ml. of water.

The entire sampling operation took about 20 seconds. The time was noted when half the pyridine solution had drained from the pipet. Temperature changes in the pyridine solution between the time it left compartment A (immersed in the bath) and the half-time of pipetting were probably not more than ±0.1°. The temperature of the room varied from 18° to 30° over the period in which the kinetic studies were made.

After eight or nine samples had been taken, the solution remaining in flask A was transferred to a small glass-stoppered bottle and placed in a dry-box for 24 hours. A sample of this was then titrated. It was assumed that reaction was complete at this time.

Treatment of Results.—The total amount of hydrochloric acid remains constant within one run, since it is also a product of the reaction being studied. The decrease of benzoylpyridinium chloride with time is evidenced by the decrease of benzoic acid. If

x = concentration of product, or benzoyl chloride reacted

a = concentration of benzoyl chloride initially

b = concentration of ester initially, and

N = concentration of titratable H^+ at time t

then

$(HCl) = a$

(H^+) due to ester $= \alpha(b - x)$

$(C_6H_5CO_2H) = a - x$

(H^+), total $= N = a + \alpha(b - x) + a - x$, and

$x = (2a + \alpha b - N)/(1 + \alpha)$ at time t

The instantaneous rate of formation of product is dx/dt. The latter was obtained from a plot of x *vs.* time. A smooth curve passing as close to as many of the points as possible was drawn using a flexible rule. A plastic 30–60° drafting triangle was placed at a point on the curve with its plane perpendicular to the plane of the paper. In proper light, the reflected portion of the curve could be lined up with that seen through the plastic triangle. When the two formed an unbroken curve, the length of the triangle was judged to be perpendicular to the curve at that point. The tangent to the curve at that point was readily found by construction.

The slope, S_0, at time $t = 0$, was difficult to obtain in the above manner. It was found empirically that a plot of log S, where S is the slope at time t, *vs.* log $(a_0 - x)$ gave a straight line. This plot was extrapolated to give S_0.

Calculation of Residual Water.—Not all of the water could be removed from the pyridine. Traces of moisture were probably picked up in transferring solutions, in spite of the precautions taken. The initial concentration of benzoyl chloride was adjusted so that it was equal to or less than that of the other reactant. At the end of 24 hours it was assumed that the reaction was complete in each case. The titration of this final reaction mixture showed that in each run some of the benzoyl chloride had apparently not reacted. The quantity of unreacted benzoyl chloride had no relation to the initial concentrations of reactants, but was of the order of magnitude expected for water as an impurity (about 0.01 *M*). It was assumed that this quantity represented the amount of water impurity present in the pyridine at the time the reactants were mixed, and that it had immediately reacted with the benzoyl chloride forming benzoic acid and pyridinium chloride. This last reaction was presumed to be very much faster than the reaction between benzoyl chloride and ethyl benzoylacetate. In the data presented in the various tables, the initial molar concentration of pyridinium chloride due to residual water is designated as x_0. The corrected or effective initial concentration of benzoyl chloride $(a - x_0)$ is designated as a_0.

Data.—One typical set of data, for run number 6, is shown in Table VI.

TABLE VI

EXPERIMENT NO. 6

$a = 0.03415$; $b = 0.02930$; N (NaOH) $= 0.04053$

t, sec.	NaOH, ml.	*N* of soln.	*x*
0		0.07080	0.00000
193	8.000	.06488	.00546
325	7.717	.06258	.00758
520	7.429	.06025	.00973
740	7.172	.05816	.01166
967	7.054	.05721	.01252
1263	6.920	.05612	.01352
1926	6.661	.05402	.01547
∞	5.694	.04616	.02273

LAWRENCE, KANSAS

---

[27] J. Timmermans, "Physico-chemical Constants of Pure Organic Compounds," Elsevier Publishers, New York, N. Y., 1950, p. 569.