sponding pyrrolidone-2 or piperidone-2 by treatment with hydrogen over Raney nickel at 200–220°.

When diethyl glutarate, or diethyl β-methyl- or β-phenyl-glutarate, was heated with four moles of a primary amine at 250°, amides were formed to the extent of 83–94%. When diethyl β,β-dimethylglutarate was so treated, yields of 39–71% of the glutarimides were formed.

Glutarimides were formed in yields of 42 to 62% by heating glutaric, β-methyl- or β-phenylglutaric acid with one mole of primary amine at 250°. This is appreciably less than the yields of succinimides obtained from succinic acid and primary amines.

An improved method for preparing diethyl glutarate has been developed.

MADISON, WIS. RECEIVED OCTOBER 1, 1936

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Rates of Alcoholysis of Acyl Chlorides

G. E. K. BRANCH AND A. C. NIXON

We have recently published the results of a study[1] in which we investigated the effect of the para-substitution of certain groups on the rates of alcoholysis of triphenylmethyl chlorides. In this paper we pointed out that predictions concerning rates in which I and T effects are used merely on the direction of electrical forces tending to prevent or assist the separation of an ion are not necessarily sound, although the actual results we obtained with the trityl chlorides could have been predicted on this basis. As we strongly suspected that this crude method of using I and T effects would be entirely erroneous when applied to the alcoholysis of acyl chlorides, we have used an identical method to measure the rates of alcoholysis of some acyl chlorides. The compounds studied are mainly para substituted benzoyl chlorides but measurements on some aliphatic compounds are also included.

We employed the same solvent as before, namely, a mixture containing by volume at 25°, 60% ether and 40% absolute ethyl alcohol. The reactions were followed by observing the rate of change of the electrical conductivity of solutions containing acid chloride. This method was used on the assumption that the hydrochloric acid produced had a much higher conductivity than any of the other constituents of the solution and hence the concentration of the acid could be determined from the conductivity of the solution by reference to a previously determined conductivity–concentration curve for hydrochloric acid. The concentration of the organic chloride at any time could then be determined as the difference between the hydrochloric acid concentration at that time and the final hydrochloric acid concentration after completion of the reaction. This method is very suitable for measuring low concentrations. We used concentrations around 0.001 *M*, and could follow the reactions accurately to more than 95% completion.

The reaction was found to be irreversible at the concentrations used since the conductivity of a 0.001 *N* hydrochloric acid in the alcohol–ether mixture was found to be unchanged by the addition of an equivalent quantity of ethyl *p*-nitrobenzoate. The irreversibility of the reaction has been shown more definitely by Norris and his co-workers,[2] who showed that ethyl *p*-nitrobenzoate was unaffected when hydrogen chloride gas was bubbled through the molten ester. Their tests also showed the absence of side reactions.

A detailed description of the method and apparatus used is given in our previous communication.[1] The method consisted essentially of mixing 20 cc. (25°) of alcohol with 30 cc. (25°) of an ether solution of the chloride at the bath temperature and then measuring the resistance of the solution at convenient intervals. The cell resistance was determined by means of the usual Wheatstone bridge arrangement, an a. c. galvanometer being used as a null instrument.

Preparation of Materials

(a) Alcohol and Ether.—These were prepared as reported previously and had within limits of error the same physical constants.

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[1] A. C. Nixon and G. E. K. Branch, THIS JOURNAL, 58, 492 (1936).

[2] J. F. Norris, E. V. Fasce and C. J. Staud, *ibid.*, 57, 1415 (1935).

(b) Acid Chorides.—These were obtained, whenever available, by distillation and/or crystallization of the Eastman product. In the other cases they were prepared from the pure acids by use of thionyl chloride. The melting and/or boiling points are given below. The boiling points are at 760 mm. unless otherwise specified.

Chloride	°C.
Trichloroacetyl	117-118 (b. p.)
Dichloroacetyl	108 (b. p.)
Chloroacetyl	106 (b. p.)
Acetyl	55 (b. p.)
p-NO_2-benzoyl	71.5 (m. p.)
p-F-benzoyl	70–71 (6 mm.), 8–9 (m. p.)
p-Br-benzoyl	37.5 (m. p.)
p-I-benzoyl	64.5 (m. p.)[a]
p-CH_3-benzoyl	70–71 (4 mm.)
p-CH_3O-benzoyl	21 (m. p.), 144 (b. p.)

[a] The melting points given for this compound in Beilstein range from 71 to 83° but repeated crystallization from hexane and sublimation did not change this value. It was prepared from two different lots of Eastman *p*-I-benzoic acid (m. p. 278°). It yielded 99.9% of the theoretical quantity of the methyl ester (m. p. 114.5–115.5°).

All the acid chlorides gave, within the limits of error, the theoretical quantity of hydrochloric acid upon alcoholysis as measured by conductivity.

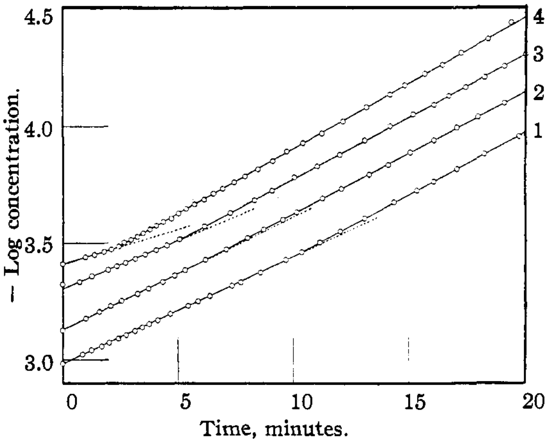


Fig. 1.—The alcoholysis of *p*-nitrobenzoyl chloride. The initial concentrations were (1) 0.00104 *M* *p*-NO_2-benzoyl chloride, (2) 0.000474 *M* *p*-NO_2-benzoyl chloride, (3) 0.000474 *M* *p*-NO_2-benzoyl chloride, 0.000493 *M* HCl, (4) 0.000388 *M* *p*-NO_2 benzoyl chloride, 0.001636 *M* HCl. The points for run (2) have been lowered by 0.2 unit. The curves are ruled lines, the dotted curves being the continuations of the ruled lines through the earlier points.

Kinetics

When the logarithms of the concentrations of the acid chlorides were plotted against the elapsed times, the straight lines characteristic of unimolecular and pseudo-unimolecular reactions were not obtained for the aromatic chlorides. Instead a plot was obtained in which the earlier points fall on one straight line and the later points on another straight line of slightly greater slope, the transition between the two being sharp. The curves in Fig. 1 for *p*-nitrobenzoyl chloride are typical examples. In Fig. 1 the negative logarithms have been plotted, so that the slopes have the same signs as unimolecular rate constants. It would appear that after some time the reaction settles down to a simple pseudo-unimolecular type. We have therefore used the final slopes multiplied by 2.303 for comparing the relative rates of reaction of the various acid chlorides. Norris and his co-workers[2] using 100% alcohol and higher concentrations of acid chlorides found the reactions to be pseudo-unimolecular over their entire course. Our conditions differ from those of Norris and co-workers since we diluted the alcohol with ether and used much smaller concentrations of acid chloride. The difference in the kinetics observed probably arises from the fact that under the conditions employed by Norris considerable hydrochloric acid had already been formed at the time of even the earliest measurements. Thus in the table given by Norris, Fasce and Staud[2] the concentration of hydrochloric acid at the time of the first measurement is 0.005 *N*, while in our experiments the first measurements are only about a hundredth of this value and the final concentrations of hydrochloric acid do not exceed 0.0021 *N*. The conditions used by Norris and co-workers, resulting as they do in simpler kinetics, are better than ours for obtaining relative rates. On the other hand, our conditions might shed some light on the beginning kinetics of the reaction. However, we do obtain approximately the same values for the relative rates of reaction as did Norris for those compounds which are common to both investigations (see Table II).

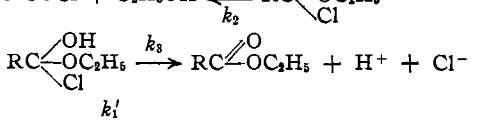
In seeking an explanation of the effect we must first eliminate the possibility that it is due to experimental error. The most obvious explanation would be that it is due to a lowering of the temperature on mixing the two solutions which would result in a smaller rate at the beginning of the reaction; however, this explanation is not tenable since the effect occurs with compounds whose reactivity is so small that several hours elapse before the final rate is attained. It could be caused by differences between the conductivities of the reaction mixture and those of the standard hydrochloric acid solutions having the same concentrations of hydrochloric acid. These differences might be due either to the conductivities of the acid chloride and ester or, more likely, to their effects on the conductivity of hydrochloric acid. The conductivity of the ester and its effect on the conductivity of hydrochloric acid is easily shown to be quite negligible, at the concentrations we employ, by direct test; but it is impossible to determine directly the effect of the acid chloride since it begins to react immediately. But, irrespective of any effect of this kind, near the end of the reaction the concentration of acid chloride is so small that its effect on the conductivity must be negligible and the observed conductivities must be correct. If the reaction is strictly first order, an extrapolation of the later portion of the curve to zero time should give the initial concentration of the acid chloride, whatever errors had been introduced in the earlier measurements. Such an extrapolation always gives an erroneously high value of the initial concentration. This shows that a real delay in the formation of hydrochloric acid occurs in the earlier stages of the reaction. In the case of acetyl chloride in which no variation from first order was observed, this extrapolation gives the correct value for the initial concentration of acid chloride.

It is unlikely that the delay could be caused by impurities in the solvents such as peroxide or water since runs performed immediately after careful redistillation of the alcohol and ether gave the same results. It is also improbable that it is due to an impurity in the acid chloride since recrystallization produced no change in the effect and the addition of a small amount of the most likely impurity, the organic acid, similarly produced no change.

p-Nitrobenzoyl chloride was selected as a typical compound to use in investigating the rate changing effect and numerous runs were made with this compound under varying conditions. The average value of the constants from the initial slopes for ten runs at concentrations varying between 0.004 to 0.0021 molal was 0.1103 reciprocal minutes, having a mean deviation of 2.5% with a maximum deviation of 4.8%, while the average value for the final constant in 14 runs in the same concentration range was 0.1223 reciprocal minutes, with a mean deviation of 2.0%, the greatest deviation being 3.6%. The position of the transition point decreased from 78% completion in the most dilute solution to 31% completion for the most concentrated solution. The average values of the final constants include those of four runs in which hydrochloric acid was added initially; the values of the initial constants for these runs are not included in the former average. Hydrochloric acid has a slight catalytic effect on the reaction, not noticeable in a single run but appearing as a slight increase in the values of the final rate constants as the initial concentration of either acid chloride or hydrochloric acid is increased. Thus five runs with *p*-nitrobenzoyl chloride at 25° having an average concentration of 0.0008 *M* have an average value for k_f of 0.1205, whereas five runs having an average concentration of 0.0019 *M* show an average value for k_f of 0.1249.

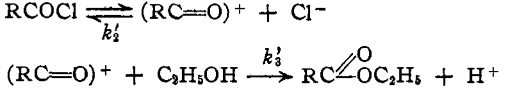
When hydrochloric acid is added initially the initial rate is decreased but the final rate is attained much earlier in the reaction. This is illustrated by plots 2 and 3 in Fig. 1. In run 3 the initial concentration of *p*-nitrobenzoyl chloride was 0.000474 *M* and of hydrochloric acid 0.000493 *M*, which gave an initial constant of 0.088 and a final constant of 0.120, the change occurring at 29% completion, whereas run 2 which started with an identical quantity of acid chloride but no hydrochloric acid gave a value of 0.114 for the initial constant and 0.119 for the final constant, the change occurring at 44% completion. With larger proportions of hydrochloric acid the effect was more pronounced; run 4, in which the initial concentration of *p*-nitrobenzoyl chloride was 0.000388 *M* and of hydrochloric acid 0.001636 *M*, gave 0.069 for the value of the initial constant and 0.127 for the final constant, the transition occurring at 15% completion.

We believe that the results given above may be interpreted on the basis of a mechanism which involves two reaction paths for the acid chloride. This may be expressed as follows

(1)


$$\mathrm{RCOCl} + \mathrm{C_2H_5OH} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{RC(OH)(OC_2H_5)Cl}$$

$$\mathrm{RC(OH)(OC_2H_5)Cl} \xrightarrow{k_3} \mathrm{RC({=}O)OC_2H_5} + \mathrm{H^+} + \mathrm{Cl^-}$$

(2)


$$\mathrm{RCOCl} \underset{k_2'}{\overset{k_1'}{\rightleftharpoons}} (\mathrm{RC{=}O})^+ + \mathrm{Cl^-}$$

$$(\mathrm{RC{=}O})^+ + \mathrm{C_2H_5OH} \xrightarrow{k_3'} \mathrm{RC({=}O)OC_2H_5} + \mathrm{H^+}$$

If the reaction follows the mechanism outlined above the rate of formation of products would be given by the equation

$$dP/dt = k_1(A)k_3/(k_2 + k_3) + k_1'(A)k_3'/(k_2' + k_3')(\mathrm{Cl}^-)$$

where (A) represents the concentration of acid chloride at any time after the intermediates have reached a steady state concentration. The first term on the right-hand side of the equation represents rate of formation of products through path (1) and the second term the contribution through path (2). The formation of products through path (1) increases in rate until a steady state concentration ratio of intermediate to reactant is reached, the value being $k_1/k_2 + k_3$. If the reaction forming the intermediate, and its reverse, are catalyzed by hydrogen ion but the change from intermediate to product is not, the period over which the velocity constant for path (1) increases is prolonged. Constancy is reached when k_3 becomes negligible with respect to k_2, and $k_1/k_2 + k_3$ becomes equal to K_e, the equilibrium constant for the change of reactant to intermediate. There is thus a limited catalysis by hydrogen ion as is shown by the trend in the final rate constants with increase in final concentration of hydrochloric acid. The final rates which we have obtained are probably a little lower than the maximum rates beyond which the reaction is not increased by acid. The contribution to the reaction by the second path diminishes with hydrochloric acid, and eventually is negligible. The reaction by path (1), were it the only source of electrolyte, would show a short induction period, followed by a more prolonged approach to a maximum rate. The induction period is masked by the reaction by path (2), which is then at its maximum, and the slow rise to a maximum rate of path (1) is to some extent compensated by the falling off in the rate by path (2). These factors tend to make the change from one value of $d \ln c/dt$ to another abrupt. Further, the vagaries of $d \ln c/dt$ that may exist in the earlier part of the reaction are not observable, as the accuracy is not sufficient to allow its evaluation between adjacent measurements, and one is reduced to using the slopes of the best straight lines drawn through the several points on the curve of log c against time. The apparent first order character of the earlier portion of the reaction is best considered fictitious. We do, however, believe that the lines shown in the figure are drawn through a sufficient number of points to warrant the statement that the earlier part of the reaction is slower than the later part beyond any reasonable doubt. The first order rate constants, heats of activation and probability factors which we obtain by ignoring the first part of the reaction are those for the reaction by path (1). If our theory is correct, Norris and his co-workers must also have obtained the rate constants for the reaction by path (1).

The Effects of Substituent Groups

The first order final rate constants at 0 and 25° in reciprocal minutes are given in columns 2 and 3 of Table I for all compounds for which these quantities could be obtained. The table also gives the heats of activation and the logarithms of the probability factors in the Arrhenius equation, $k = Ze^{-E/RT}$.

Table I

Reaction Rates and Heats of Activation

The values of log Z were calculated by the use of the equation $\log Z = \log k^{25} + E/2.3\,KT$, in which k^{25} is in reciprocal seconds.

Chloride	k^0, min.$^{-1}$	k^{25}, min.$^{-1}$	E, cal.	Log Z
Trichloroacetyl	(>5)	.....	....	...
Dichloroacetyl	(>5)	.....	....	...
Chloroacetyl	2.89	.....	....	...
Acetyl	0.143	0.986	12,500	7.4
p-NO_2-benzoyl	.0222	.1225	11,100	5.5
p-Br-benzoyl	.00167	.0134	13,450	6.2
p-Cl-benzoyl	.00145	.0123	13,850	6.5
p-I-benzoyl	.00158	.0126	13,450	6.2
p-F-benzoyl	.000761	.00732	14,650	7.8
Benzoyl	.000700	.00648	14,400	6.6
p-CH_3-benzoyl	.000332	.00386	15,900	7.5
p-CH_3O-benzoyl	.000180	.00320	18,650	9.4

Table II

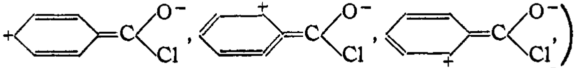
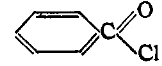
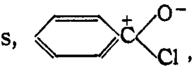
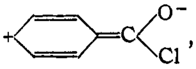
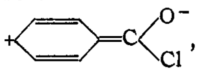
Relative Rates of Alcoholysis at 25°

Chloride	Relative rates in alcohol-ether	Relative rates in absolute alcohol	Relative rates of corresponding trityl chlorides
Trichloroacetyl	(>8000)	..	....
Dichloroacetyl	(>8000)	..	....
Chloroacetyl	(4100)	..	....
Acetyl	171	..	0.00007
p-NO_2-benzoyl	19.0	21.6	.011
p-Br-benzoyl	2.1	2.1	.28
p-Cl-benzoyl	1.9	1.9	.32
p-I-benzoyl	1.9	1.9	.34
p-F-benzoyl	1.1	..	.76
Benzoyl	1.0	1.0	1.0
p-CH_3-benzoyl	0.60	0.78	4.1
p-CH_3O-benzoyl	.49	.81	(>90)

From the data of Table I we have constructed Table II which gives the rates of alcoholysis, at 25°, relative to benzoyl chloride. In column 3 are given the values determined by Norris and co-workers, of the relative reactivities of a number of the same acid chlorides for the reaction in absolute alcohol. It also gives, in column 4, the rates of alcoholysis, relative to triphenylmethyl chloride, of a number of para substituted triarylmethyl chlorides the substituent groups of which are the same as the groups substituted in the benzoyl chlorides, the compounds in each row having the same substituent. Thus the rate of alcoholysis of *p*-nitrotriphenylmethyl chloride relative to that of triphenylmethyl chloride is put in the same row as the relative rate of *p*-nitrobenzoyl chloride. We have taken diphenylmethyl chloride as the analog of acetyl chloride.

It is noticed that the order we have obtained for the relative rates of alcoholysis of the acyl chlorides parallels the order obtained by Norris, except that in our solvent *p*-methoxybenzoyl reacts less rapidly than *p*-methylbenzoyl chloride, while in absolute alcohol the two reactions have approximately the same rate.

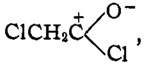
A comparison of columns 2 and 4 in Table II shows that a para substituent affects the alcoholysis of aryl acid chlorides and triarylmethyl chlorides in opposite ways. Groups that increase the rates of alcoholysis of the acid chlorides decrease those of trityl chlorides. In our preceding paper we have shown that in the trityl chlorides the influence of the para substituent follows the ability of the group to transfer a positive charge from the methyl carbon atom to the other parts of the molecule. In this way the groups assist the removal of chloride ion, and increase the rates of alcoholysis. The alcoholysis of a chloride involves not only the removal of chloride ion, but also the addition of alcohol. The influence of the group on the addition of alcohol may be opposite to its effect on the removal of chloride ion, and may be the predominant factor governing the relative rates of alcoholysis. The existence of these two factors is obvious in our suggested equation for the rates, rate = $K_e k_3 A$, in which K_e is the equilibrium constant for an addition of alcohol and k_3 the rate constant for the decomposition of the addition compound into hydrochloric acid and ester. The effect of a para substituent group on k_3 must be assumed to be in the same direction as its effect on the alcoholysis of a trityl chloride, though its magnitude may be much less, as the removal of the chloride ion is largely assisted by the tendency of the unshared electrons of the oxygen atoms to relieve the lack of electrons induced on the carbonyl carbon atom by the removal of chloride ion.

The effect of a para substituent group on K_e is best understood if one uses the combination formula,   instead of the classical formula . The above resonance stabilizes the acid chloride, and does so to a greater degree the more stable the internally ionized structures, , , etc., are. In this way the resonance decreases K_e, as it is absent or negligible in the addition compound. Any para substituent which by the direction of its group dipole or by a resonance increases the stability of the structure , decreases the value of K_e. Examples of such groups are CH_3 and OCH_3. On the other hand, strongly negative groups increase the value of K_e. In this way the effect of a para substituent on K_e is opposite to its effect on the velocity constant of alcoholysis of a trityl chloride, or on k_3.

Whether the effect of a para substituent on K_e or on k_3 will be the predominant factor in the alcoholysis can only be decided by experiment. Our experiments show that the first factor is predominant for groups having effects within the range studied. Outside of this range it is possible for the influence on k_3 to become the predominant factor, in which case the order of alcoholysis rates of the acid chlorides would follow those of the trityl chlorides. This possibility is suggested in our results. The increase of rate from *p*-methylbenzoyl chloride to *p*-nitrobenzoyl chloride is thirty-fold, the increase in rate from *p*-nitrotriphenylmethyl chloride to *p*-methyltriphenylmethyl chloride is somewhat larger, about four hundred-fold, but the increase of rates from *p*-methoxy to *p*-methylbenzoyl chloride is only 20% which is very much smaller than the twenty-fold increase from *p*-methyltriphenyl chloride to *p*-methoxytriphenylmethyl chloride. Under the conditions used by Norris and his co-workers *p*-methoxybenzoyl chloride reacts as rapidly as *p*-methylbenzoyl chloride.

We have avoided consideration of ortho groups.

In these derivatives the substituent and reacting groups are brought into very close proximity, and what might be called O-effects are introduced. Norris' results and previous work on so-called "steric hindrances" indicate that O-effects are greatly enhanced by duplication. The alcoholysis rates of 2,4,6-trisubstituted benzoyl chlorides[3] have entirely different orders of magnitude to those of the monosubstituted derivatives. These trisubstituted benzoyl chlorides may react either very much faster or very much slower than the monosubstituted compounds.

The work on the trityl chlorides shows that the phenyl group can lower the positive potential of an adjacent atom more than the methyl group can. Assuming that the addition of alcohol is still the predominant factor, the alcoholysis rates of aliphatic acid chlorides should be faster than those of the aromatic. In chloroacetyl chloride the potential energy of the internally ionized form,  $ClCH_2\overset{+}{C}\begin{matrix}\diagup O^- \\ \diagdown Cl\end{matrix}$, is increased by the dipole of the α-chlorine atom, its + pole being directed toward the carbonyl carbon atom. This decreases the resonance, and increases the rate of alcoholysis. Further introduction of chlorine atoms should still further increase the rate. These relationships were found, except that di- and trichloroacetyl chlorides reacted so rapidly that it was impossible to determine which was the more reactive.

Heats of Activation

The heats of activation given in Table I were calculated from the values of the final rate constants determined at 0 and 25° by solving for E in the equation $\ln k = \ln Z - E/RT$.

There is a rough correlation between low activation energy and rapid reaction in the alcoholysis of the acid chlorides. In the aromatic compounds the differences in the rates cannot be attributed only to the differences in the heats of activation. In general the differences in the rates are much smaller than would be expected from the differences in the activation energies. This can be seen by comparing the probability factors (Z). These show a trend, being higher for the slower reactions. For instance, if we divide the reactions into four classes, (1) the very fast reaction, that of *p*-nitrobenzoyl chloride, (2) the moderate reactions, those of para Cl, Br and I benzoyl chlorides, (3) the slow reactions, those of *p*-F and benzoyl chlorides, and (4) the slowest reactions, those of *p*-CH_3 and OCH_3, the average values of log Z for these classes are 5.5, 6.3, 7.2 and 8.4. Although errors accumulate in the determination of Z, this trend lies well beyond the experimental limits. In the alcoholysis of the trityl compounds this trend is not noticeable, the figures for the corresponding compounds, in that series, being 8.4, 7.5, 7.9 and 8.0. (The value for the methoxy compound was not obtained.) For acetyl chloride the value of log Z is 7.4, that is, the value is much higher than that of the slower reacting *p*-nitrobenzoyl chloride. The value of E is also greater for acetyl chloride than it is for the nitrobenzoyl chloride, the difference being greater than any likely experimental error.

The values of Z for the alcoholyses of the acid chlorides are much less than those usually found for reactions of ions with neutral molecules. The alcoholyses of acid chlorides belong to Moelwyn-Hughes' class of slow reactions.

Summary

The rates of alcoholysis of several acyl chlorides have been measured, at great dilutions, in a mixture of 60% ether and 40% alcohol.

The kinetics of the reaction and the relative reactivities of the acyl chlorides are discussed.

BERKELEY, CALIF. RECEIVED SEPTEMBER 8, 1936

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[3] J. F. Norris and H. H. Young, THIS JOURNAL, **57**, 1420 (1935).