Aspects of Tautomerism. Part 15.[1] Investigations on Oxo-participation in δ-Oxocarboxylic Acid Chlorides during their Formation and Alcoholysis

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Oxalyl chloride converts ring-substituted 4-benzoylbutyric acids into a mixture of normal and pseudo-acid chlorides by two independent and competing pathways. Pseudoacid chlorides are formed by a concerted $2_\sigma + 2_\pi + 2_\sigma$ pathway. It is suggested that the reaction of acid chlorides with a poor nucleophile involves a transition state wherein the attacking nucleophile and the departing group make an angle of *ca.* 45° to the plane of the carbonyl group. There is evidence against involvement of any common transition state or an equilibration process during the formation of normal and pseudoacid chlorides. Alcoholysis of normal acid chlorides derived from the above mentioned acids does not involve oxo-participation.

γ-Oxoacids as a rule form exclusively pseudoacid chlorides.[2] There are only two γ-oxoacids which are exceptions to this rule.[2] δ-Oxoacids, on the other hand, give a mixture of pseudo and normal isomers. The reagent used apparently does not have a bearing on the nature of the product. It is not clear from the literature whether there is an equilibrium between the two forms in the case of δ-oxoacid chlorides.

We report an investigation into the factors which govern pseudoacid *versus* normal acid chloride formation. We believe that this question is linked to the more fundamental problem of the stereochemistry of substitution at the carbonyl carbon and the nature of the transition state involved therein.

In the present work we have converted variously ring-substituted δ-benzoylbutyric acids into their acid chlorides using oxalyl chloride and determined the proportion of the two isomers formed. Also we have studied the alcoholysis of the normal acid chlorides to find out whether there is oxo participation during solvolysis.

Results and Discussion

4-Benzoylbutyric acid and its four ring-substituted derivatives (**1a—e**) (R = *p*-OMe, *p*-Me, *p*-Br, and *m*-NO_2) were treated with oxalyl chloride and the resulting products were analysed by ^{1}H n.m.r. spectroscopy. It was found that during their formation pseudoacid chlorides underwent dehydrochlorination to yield the corresponding enol lactones[3] (**4a—e**). Accordingly, the proportions of enol lactones and normal acid chlorides were estimated. Also, the mixture of products was treated with aqueous ammonia and the resulting products consisting of enol lactone and the amide were separated and their proportions computed. These results are summarized in Table 1.

From Table 1 it is clear that when electron-withdrawing groups are present they favour the formation of a larger proportion of enol lactone and the parent acid chloride at the expense of the normal acid chloride. The opposite situation prevails when electron-donating groups are present. These results would clearly rule out the involvement of an equilibrium process during the reaction of the above mentioned acids with oxalyl chloride. Further these results indicate that pseudoacid chloride formation is a competing pathway during the conversion of δ-benzoylbutyric acid into the normal acid chloride (Scheme 2). Data presented in this paper together with those in the literature permit the following conclusions.

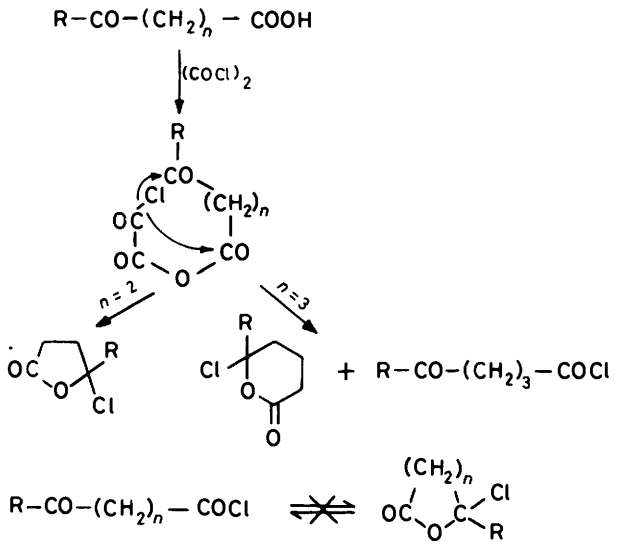
(i) Oxoacids give pseudoacid chlorides only when their formation is kinetically favoured over that of the normal acid chlorides and not because of any constraints on the formation of normal acid chlorides.

(ii) The γ-oxo function presents an ideal neighbouring group for a concerted attack by the oxo oxygen on the carboxy carbon when it is being subjected to nucleophilic attack by

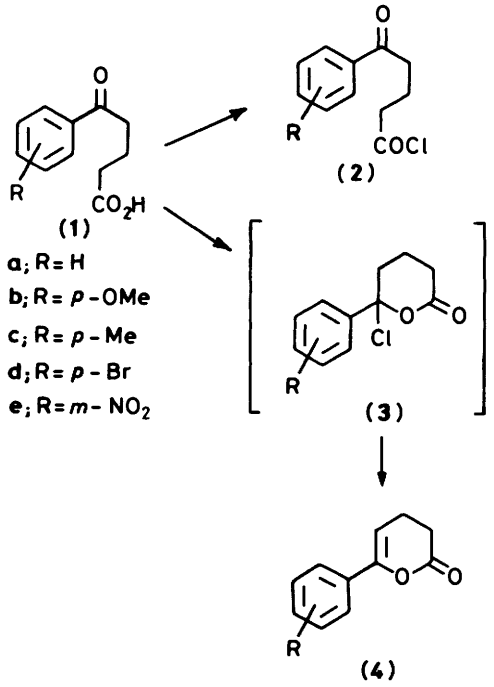
Table 1. Yields of the normal acid chloride and enol lactones formed from substituted benzoylbutyric acids (**1a—e**)

Compound	Yield by ^{1}H n.m.r. analysis[a] % Lactone	% Acid chloride	Isolated yield % lactone
(**1b**)	*b*	*b*	8.7
(**1c**)	19.8	80.2	13.1
(**1a**)	21.0[c]	79.0[c]	15.5
(**1d**)	36.8	63.2	32.1
(**1e**)	55.0	45.0	32.0

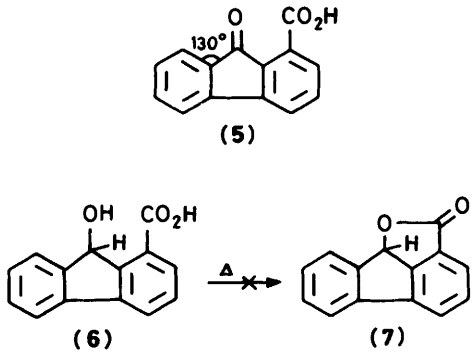
[a] Olefinic proton signal was observed near δ 5.8. Percentage of lactones and normal acid chlorides were computed using peak areas. [b] No signal due to olefinic proton was observed as the amount of lactone was very low in the mixture. [c] Unaffected after treatment with lithium chloride.



Scheme 1.



Scheme 2.



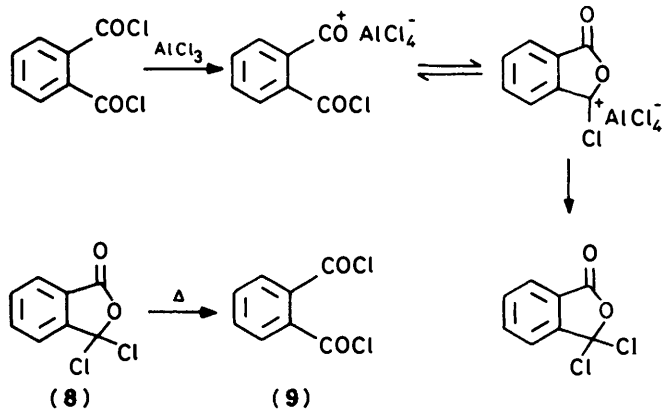
Scheme 3.

chloride. The geometrical requirements of this type of transition state are present optimally in γ-oxoacids.

(iii) In δ-oxoacids although this type of transition state is possible, bringing the oxygen end of the carbonyl group to the bonding distance of the carboxy group and keeping it aligned against the considerations of entropy seems to make such a transition state favoured to a smaller extent than in the case of γ-oxoacids.

A corollary of this analysis is that the structural features of γ-ketoacids, which (a) make it difficult to bring the oxo oxygen near the carbonyl carbon or (b) which prevent or hinder the attack by the chloride on the carbonyl carbon, should disfavour pseudoacid *versus* normal acid chloride formation.

Fortunately the literature provides one example of each of these situations.[2-4] 9-Oxofluorenecarboxylic acid (**5**) is one of the γ-oxoacids which does not give a pseudoacid chloride. A failure to form the pseudoacid chloride could be recognized as arising due to the difficulty in bringing the carbonyl group to the bonding distance of the carboxy carbon, at an angle appropriate for bimolecular nucleophilic displacement.* Support for this view comes from the fact that the corresponding alcohol, 9-hydroxyfluorene-1-carboxylic acid (**6**), does not form the



Scheme 4.

lactone (**7**) whereas in the case of analogous *o*-benzoylbenzoic acid, the hydroxy acid cannot be isolated except as its metallic salt and the reduction of the oxoacid yields the lactone as the only isolable product.[5]

The failure of *o*-mesitoylbenzoic acid to form the pseudoacid chloride arises from the severely decreased accessibility of the carbonyl group for a lateral attack by the chloride. In mesitoyl derivatives steric hindrance at the carbonyl carbon is well documented. If the carbonyl group were to be in the plane of the aromatic ring and if its nucleophilic reaction were to take place from the direction of the π cloud, there should be no steric hindrance. But it has been established that the carbonyl group orients out of the plane of the aromatic ring and consequently the approach of the nucleophile to the carbonyl group is hindered. Hence pseudoacid chloride formation is not observed in this case also.

From the foregoing it is clear that the formation of the pseudoacid chloride is a concerted reaction involving a carboxylic acid derivative, a oxo group, and the halide. In modern terminology it is a $2_\sigma + 2_\pi + 2_\sigma$ concerted reaction. Newmann and his co-workers[4,6] who recognized this reaction as one involving a distinct type of transition state have designated it as a [3.2.1]bicyclic pathway.

Thermal isomerization of pseudo (**8**) to normal (**9**) phthaloyl chloride[7] is another concerted reaction of acid chlorides. It can be considered as the reverse of the reaction of the normal acid chloride with nucleophiles. Both these reactions may be expected to go through analogous transition states. Phthaloyl chloride isomerization is a thermal $2_\sigma + 2_\sigma$ concerted reaction that goes through a non-planar transition state (Scheme 4).

The reaction of acid chlorides with nucleophiles is basic to organic chemistry and has attracted a great deal of investigation. In spite of this some of the main issues are not defined, *e.g.* (a) the stereochemistry of displacement *i.e.*, geometry of the transition state and (b) the conditions and structures which favour addition–elimination, S_N1, or S_N2 types of displacement.

In previous papers[7,8] we presented evidence in support of our view that carboxylic acid chlorides as a rule are hydrolysed by an S_N2 pathway without involving addition–elimination. This conclusion was arrived at after studying the solvolysis of a number of normal and pseudoacid chlorides. Previously reported isotopic exchange studies[9] are clearly consistent with this view, although a number of workers continue to advocate

* A referee has suggested that decreased carbonyl reactivity, because of the better conjugation of the carbonyl group with the aromatic ring, might contribute to the absence of pseudoacid chloride.

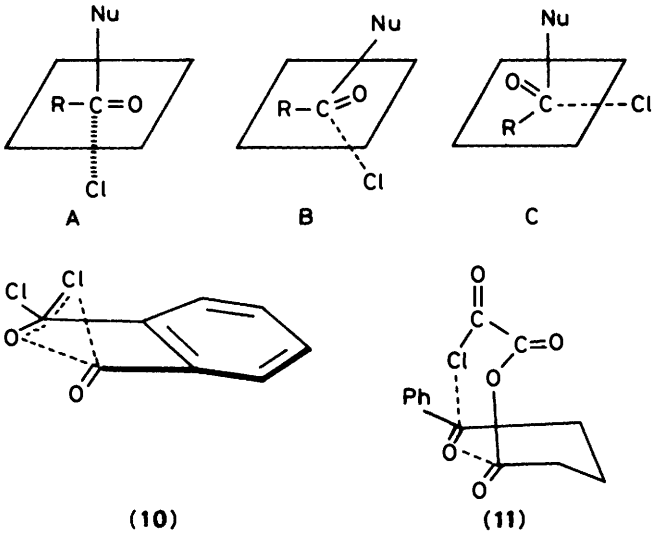


Figure.

Table 2. Pseudo-first-order rate constants for the methanolysis of ring-substituted benzoylbutyric acid chlorides (**2a**—**e**) in 50% (v/v) acetone–methanol at 30 °C

Substrate	*p*-OCH_3	*p*-CH_3	H	*p*-Br	*m*-NO_2
10^3 *k*/min^{-1}	4.75	4.66	4.80	4.60	4.66

addition–elimination and S_N1 mechanisms. A recent independent study also supports an S_N2 pathway.[10]

If the most common pattern of solvolysis is by an S_N2 mechanism not involving addition–elimination or S_N1 pathways, the question naturally arises as to the stereochemistry of the transition state. Very little information is available in the literature on this subject. Bender[11] has suggested that the carbonyl carbon in carboxylic acid derivatives may undergo nucleophilic displacement involving an approximately perpendicular attack at the carbonyl carbon. Bellard and Bamford[12] have presented a case wherein the direction of approach of the nucleophile is similar to that found in simple nucleophilic substitution at the tetrahedral carbon.

One can therefore consider three types of transition states as in the Figure, based on the data available in the literature. From the Figure it is clear that both phthaloyl chloride isomerization and pseudoacid chloride formation are not possible through either A or C. This leaves B as the only plausible transition state which can explain both concerted reactions. One can only conceive of a transition state where the oxygen end of the carbonyl group attacks the carboxy carbon at an angle of *ca.* 45°, after approaching the bonding distance. We suggest that phthaloyl chloride isomerization and pseudoacid chloride formation involve attack at the carbonyl carbon by chloride at an angle of *ca.* 45° to the plane of the carbonyl group in the transition state. This may be the general pattern for the reaction of the majority of acid chlorides with nucleophiles. A recent molecular orbital study on nucleophilic substitution in acyl chlorides also supports this view.[13]

The product composition obtained, *viz.* the proportions of the normal acid chlorides and the enol lactones, remained unaffected when stirred with lithium chloride in acetonitrile. This observation also argues against the isomerization of normal and pseudoacid chlorides after they are formed.

A study of methanolysis of ring-substituted normal 4-benzoylbutyric acid chlorides (**8a**—**e**) under pseudo-unimolecular conditions was made. All compounds solvolysed at the same rate without displaying any substituent effect (see Table 2). The acid chlorides are solvolysed by direct attack by the solvent on the acid chloride function; this means that there is no oxo-participation during solvolysis. This is contrary to our earlier finding that oxo-participation is observed during the basic hydrolysis of esters.[14]

It is well known that the carbonyl reactivity decreases in the order RCOCl > RCOR′ > RCO_2R'. The pathway involving oxo-participation takes place only when it becomes competitive, or it is faster than direct attack. If it is slower, such a pathway would not be availed of. This apparently happens in the case of normal acid chloride because direct attack is much faster than that through the keto carbonyl group.

Experimental

M.p.s are uncorrected. ^{1}H N.m.r. spectra were recorded on either Varian T60 or Varian HA 100 spectrometers. Chemical shifts are referred to internal tetramethylsilane. I.r. spectra were recorded on a Perkin-Elmer 781 spectrometer. Chromatographic separations were carried out using silica gel (60—120 mesh).

Substituted Benzoylbutyric Acids.—4-Benzoylbutyric acid, 4-(*p*-bromobenzoyl)butyric acid, 4-(*p*-toluoyl)butyric acid, and 4-(*p*-methoxybenzoyl)butyric acid were prepared by the Friedel–Crafts reaction of glutaric anhydride with benzene, bromobenzene, toluene, and anisole respectively.[15–18] 4-(*m*-Nitrobenzoyl)butyric acid[19] was prepared by the nitration of 4-benzoylbutyric acid with a mixture of concentrated sulphuric acid and fuming nitric acid (*d.* 1.42).

Acid Chlorides.—Acid chlorides of the acids mentioned above were prepared by reaction, with oxalyl chloride,[20] of the corresponding acids with catalytic amounts of dimethylformamide. Solid products (sometimes gummy solids) obtained were used without further purification. Acid chlorides were also obtained by the use of thionyl chloride, but this procedure usually gave dark coloured products. Oxalyl chloride was, therefore, used throughout the present work.

Typical procedure. 4-Benzoylbutyric acid chloride. 4-Benzoylbutyric acid (500 mg, 2.6 mmol) was stirred with oxalyl chloride (1 ml) and dry ether (2 ml) at room temperature for 6 h. Ether and excess of oxalyl chloride were removed *in vacuo*, without heating the reaction mixture (increase of temperature results in dark coloured products). The semi-solid obtained was analysed by ^{1}H n.m.r. spectroscopy.

Preparation of Dihydropyrones.—Acid chlorides obtained as above were dissolved in the minimum volume of chloroform or acetonitrile and stirred with aqueous ammonia. The enol lactones were separated by column chromatography.

Typical procedure. 3,4-Dihydro-6-phenyl-2-pyrone. Acid chloride obtained from 4-benzoylbutyric acid (500 mg, 2.6 mmol) was dissolved in chloroform (5 ml) and aqueous ammonia was added dropwise with stirring, till a faint smell of ammonia persisted.* Stirring was continued for another 5—8 min. Ammonium chloride was removed by filtration and the product

* Use of excess of ammonia and/or longer reaction times results in lower yield or total loss of material.

was chromatographed over silica column (eluant benzene), yield 70 mg (15.5%); m.p. 51—52 °C (lit.,[21] 47—48.5 °C), δ($CDCl_3$) 2.6 (m, 4 H), 5.8 (t, 1 H), and 7.5 (m, 5 H).

3,4-*Dihydro*-6-*tolyl*-2-*pyrone*. Yield 13.1%, m.p. 58—59 °C, $\nu_{max.}$(Nujol) 1 760 and 1 660 cm^{-1}, δ($CDCl_3$), 2.4 (s, 3 H), 2.6 (m, 4 H), 5.8 (t, 1 H), and 7.5 (q, 4 H).

3,4-*Dihydro*-6-(p-*methoxyphenyl*)-2-*pyrone*. Yield 8.7%, m.p. 87—88 °C, $\nu_{max.}$($CHCl_3$) 1 740 and 1 640 cm^{-1}, δ($CDCl_3$) 2.6 (m, 4 H), 3.8 (s, 3 H), 6.0 (t, 1 H), and 7.2 (q, 4 H).

3,4-*Dihydro*-6-(p-*bromophenyl*)-2-*pyrone*. Yield 32.1%, m.p. 81—82 °C, $\nu_{max.}$(Nujol) 1 760 and 1 660 cm^{-1}, δ($CDCl_3$) 2.5 (m, 4 H), 5.8 (t, 1 H), and 7.5 (m, 4 H).

3,4-*Dihydro*-6-(m-*nitrophenyl*)-2-*pyrone*. Yield 32%, m.p. 103—104 °C, $\nu_{max.}$(Nujol) 1 750 and 1 650 cm^{-1}, δ($CDCl_3$) 2.6 (m, 4 H), 5.9 (t, 1 H), and 8 (m, 4 H).

All the lactones were treated with dilute sodium carbonate solution and, on neutralization, the original acids were obtained.

Effect of Lithium Chloride on the Relative Amounts of Acid Chloride and Enol Lactone in the Mixture.—Acid chloride–lactone mixture from 4-benzoylbutyric acid (500 mg, 2.6 mmol) was dissolved in dry acetonitrile (5 ml) and stirred at room temperature with lithium chloride (100 mg, 2.3 mmol) for 12 h. The proportions of acid chloride and lactone was estimated by ^1H n.m.r. spectroscopy before and after the experiment (see Table 1).

9-*Hydroxyfluorene*-1-*carboxylic Acid*.—9-Oxofluorene-1-carboxylic acid (1 g, 4.5 mmol) was dissolved in THF (15 ml) and stirred with sodium borohydride (300 mg) for 24 h. More sodium borohydride was added at this stage (200 mg) and stirring continued for another 24 h. THF was removed by distillation, decomposed with dilute HCl, and the product extracted with ethyl acetate and the extract was dried ($MgSO_4$). A pale yellow solid was obtained (800 mg 79.3%), m.p. 190—191 °C (lit.,[22] 194—195 °C).

Pyrolysis.—9-Hydroxyfluorene-1-carboxylic acid was heated to 250 °C under vacuum for 5—10 min. A dark gummy solid was obtained (further heating resulted in charring of the compound). It was analysed by i.r. spectroscopy. No absorption for a five-membered lactone carbonyl could be detected.

Estimation of Amount of Enol Lactone and Normal Acid Chloride in Mixtures by ^1H *N.m.r.*—A signal due to an olefinic proton was observed near δ 5.8 and that due to methylene protons (lactone and acid chloride) was observed near δ 2.5. A typical calculation is shown for the *p*-bromo derivative.

Number of olefinic protons = 1
Number of methylene protons = 10 (6 due to acid chloride and 4 due to lactone)
Percentage of olefinic protons (ratio) = 1/11 × 100 = 9.09%
Area below the signal due to olefinic proton = 0.7 units
Area below the signal due to methylene protons = 10 units
Ratio of olefinic proton to methylene protons = 1:14
= 1/15 × 100
= 6.7%

If the percentage ratio is 9.09 then the mixture has 50% lactone and 50% acid chloride. If the percentage ratio were 6.7% the mixture would have 6.7 × 50/9.09 = 36.8% of the lactone.

Kinetic Procedure.—The reaction of acid chlorides with alcohols and water is described by equations (1) and (2). It is

$$RCOCl + R'OH \longrightarrow RCO_2R' + HCl \quad (1)$$

$$RCOCl + H_2O \longrightarrow RCO_2H + HCl \quad (2)$$

evident that one mole of acid chloride upon hydrolysis requires two equivalents of alkali whereas alcoholysis requires one equivalent of alkali. Thus theoretically, if Y ml of alkali is consumed by an aliquot portion at the beginning of the reaction (zero time), $Y/2$ ml will be consumed at the end (infinite time). The decrease from Y to $Y/2$ ml with time forms the basis for the measurement of the rates of alcoholysis of the acid chlorides.

Methyl alcohol was dried using magnesium methoxide. Acetone used was of GR grade. Barium hydroxide solution used for titration was stored out of contact with air. The temperature of the reaction mixture was maintained at 30 ± 0.1 °C throughout.

Acid chloride (5 mmol) was dissolved in acetone and made up to 50 ml in a standard flask. This solution (10 ml) was diluted with acetone (10 ml) and thermostatted for ½ h. Methanol (20 ml) thermostatted at the same temperature was added to the acid chloride. The solution was mixed well and 5 ml of the mixture was withdrawn without delay and quenched with aqueous acetone and titrated with standard barium hydroxide solution. This titre value gave Y. Then aliquot portions were withdrawn at known intervals, quenched, and titrated as above.

If Y_t is the volume of alkali consumed by a portion at time t, $(Y_t - Y/2)$ gives $(a - x)$. A plot of $(a - x)$ *versus* t gives a straight line with slope $-k/2.303$.

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