CXCVIII.—*The Action of Acyl Chlorides on Primary Amides.*

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ALTHOUGH the action of acyl chlorides on amides in the presence of pyridine has been closely studied by one of the authors, and by others, very little appears to be known concerning the interaction which takes place when an acyl chloride and amide are heated together. Preliminary observations which were made in the course of this investigation made it clear that the reaction was by no means simple, and that a variety of products might result the nature of which depended on the conditions of the reaction. Experiments were accordingly instituted with the object of throwing light on the mechanism of the reaction occurring between an acyl chloride and amide by selecting acetyl and benzoyl chlorides,

In a previous communication it has been shown by one of the authors (Trans., 1911, **99**, 867) that salicylamide and acetyl chloride readily react, yielding the hydrochloride of the cyclic compound $\text{C}_6\text{H}_4 \begin{smallmatrix} \text{CO} \cdot \text{N} \\ \diagup \quad | \\ \text{O} \quad \text{CMe} \end{smallmatrix}$. As this hydrochloride was, from its behaviour with aniline, at first believed to be the chloro-compound $\text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{N} \cdot \text{CMeCl}$, it appeared likely that the first stage in the reaction between a primary amide and acyl chloride might be a process of condensation leading to a chloro-compound of the type $\cdot \text{CO} \cdot \text{N} \cdot \text{CRCl}$, the water eliminated then decomposing a second molecule of acyl chloride in the usual way, thus:

it has been shown that, besides benzo-*p*-toluamide, both *p*-toluonitrile and benzonitrile (together with benzoic acid and *p*-toluic acid) may be formed. As, however, in the mixed nitriles, *p*-toluonitrile always predominates, and as it is practically the sole product when an excess of *p*-toluamide is employed, it would appear that the production of benzonitrile is not due to the above hypothetical mechanism, but is connected with some secondary decomposition, probably that of the benzo-*p*-toluamide, which, under the catalytic influence of hydrogen chloride, could decompose in two possible ways, thus:

A similar decomposition has been observed with dibenzamide, which at 140°, under the catalytic influence of hydrogen chloride, yields benzonitrile and benzoic acid; and in further support of this view it has been found that in the reaction between *p*-toluamide and benzoyl chloride, under varying conditions, the yields of secondary amide and benzonitrile are inversely related, that is, benzonitrile is formed at the expense of a diminished yield of benzo-*p*-toluamide. Thus, at 140°, when three molecular proportions of *p*-toluamide to one of benzoyl chloride are taken, a considerably higher yield of benzo-*p*-toluamide (with practically no benzonitrile) is found than when equimolecular proportions are taken (a considerable quantity of benzonitrile being formed). This difference is to be attributed to the fixation of the hydrogen chloride by the amide when an excess of the latter is used, yielding *p*-toluamide hydrochloride, $\text{C}_6\text{H}_4\text{Me}\cdot\text{CO}\cdot\text{NH}_2\cdot\text{HCl}$, which was isolated in quantity.

In general, the facts established make it clear that in the action of benzoyl chloride on an aromatic amide two distinct reactions occur, one (to a relatively small extent) leading to direct benzoylation, and the other to what is virtually dehydration, thus:

That reaction *B* is independent of *A*, and that the production of nitrile and acid does not mainly arise by secondary decomposition of the secondary amide first formed, appears to follow from the fact that even when an excess of amide is taken and the hydrogen chloride (which alone is effective in causing decomposition of the

secondary amide) is largely fixed, the actual amount of secondary amide is still small.

No appreciable reaction occurs below 100°, and the influence of increasing temperature is greatly to increase the apparent velocity of reaction *B* and depress the yield of secondary amide, the reaction being complete at 140° in six hours. This easy dehydration of aromatic amides is probably not a direct reaction, but one in which an unstable benzoyl derivative of the imino-ester type (III) is first formed by benzoylation of the pseudomeric form of the amide (II), benzoic acid being subsequently eliminated:

On the other hand, the production of secondary amide may be attributed to direct benzoylation of the normal amide form ($\cdot\text{CO}\cdot\text{NH}_2$) by loss of hydrogen chloride from the intermediate hypothetical additive compound (IV).

If this view is correct, the low yields of secondary amide must be attributed to a higher chemical activity of the pseudomeric form in the equilibrium mixture:

but it is impossible at present to say how far the reduced yield of secondary amide at higher temperature is due to higher concentration of the pseudomeric amide or to the catalytic decomposition of the former by hydrogen chloride. Experiments will be instituted to throw light on the nature of the decomposition by hydrogen chloride of mixed secondary amides.

Owing to the above simultaneously occurring changes in the action between *p*-toluamide and benzoyl chloride, the following products appear in varying proportions according to the conditions: *p*-toluamide hydrochloride, *p*-toluonitrile, benzoic acid, and benzo-*p*-toluamide, together with benzonitrile and *p*-toluic acid. The amount of the last compound was usually more than would be expected to arise by the decomposition of benzo-*p*-toluamide, and, further, ammonium chloride was also found. These two substances appear to arise from a secondary decomposition between *p*-toluamide hydrochloride and hydrogen chloride, and, in order to elucidate this point, the action of hydrogen chloride on benzamide and *p*-toluamide was investigated. Both these amides readily yield hydrochlorides as white, crystalline solids, which dissociate incompletely at 140°, and are somewhat soluble in benzoyl chloride. When heated at 140° for several hours in an atmosphere of hydrogen

chloride, they are largely decomposed, giving ammonium chloride and the corresponding acyl chloride, which then reacts as above with a portion of the dissociated free amide, so that varying mixtures may result containing ammonium chloride, acyl chloride, acid nitrile, and secondary amide, according to the duration of heating. This decomposition is probably preceded by the formation of an additive compound (V) of amide and hydrogen chloride, involving opening up of the carbonyl group, thus:

This action at once explains why *p*-toluic acid and ammonium chloride appear in the reaction between benzoyl chloride and *p*-toluamide. Di-*p*-toluamide, which should also be produced, was not detected, probably on account of its small quantity.

The action of benzoyl chloride on acetamide, which has already been the subject of study by Pinner (*Ber.*, 1892, **25**, 1435) and one of the authors (*Trans.*, 1901, **79**, 412), follows on a similar mechanism (*B*) to that of benzoyl chloride on aromatic amides, without production of secondary amide, but it takes place with very much greater velocity, and is nearly complete at 80° in five minutes, yielding acetonitrile (which polymerises slightly) and benzoic acid, together with acetamide hydrochloride in large quantity. It is thus evident that the velocity of reaction *B*, involving condensation with the pseudomeric form of acetamide, is enormously higher than the corresponding reaction with aromatic amides. Small quantities of benzoic anhydride are also found as a by-product, and its origin has been traced to a secondary action between benzoyl chloride and benzoic acid under the influence of acetamide as a remover of hydrogen chloride. Benzoic anhydride has been shown by the authors to be formed in moderate quantity, even in absence of acetamide, by the action of benzoyl chloride on benzoic acid at 80°, by the reversible change:

but the yield, as might be expected, is greatly increased by the presence of acetamide. This observation is in accordance with the fact established by Brooke (*J. Amer. Chem. Soc.*, 1912, **34**, 492), that acetyl chloride and acetic acid, by a reversible reaction, yield small quantities of acetic anhydride; whilst conversely the authors have observed that acetic anhydride is rapidly decomposed in the cold by hydrogen chloride, yielding acetyl chloride and acetic acid.

The action of acetyl chloride on simple amides differs from that of benzoyl chloride in that it takes place more readily and leads mostly to acetylation, thus:

This has already been shown to be the case by one of the authors with acetamide (Titherley, Trans., 1901, **79**, 411). It has now been shown that a considerable yield of acetobenzamide is produced by the continued action of acetyl chloride, at its boiling point, on benzamide. No evidence of any intermediate chloro-compound could be obtained by examination of the product after treatment with aniline, but traces of benzanilide were found showing the presence of benzoyl chloride. The production of benzoyl chloride evidently arises as a secondary decomposition between benzamide hydrochloride and hydrogen chloride, as already discussed.

EXPERIMENTAL.

Benzoyl Chloride and Benzamide.

The two substances were heated together in a reflux apparatus, moisture being excluded by means of a phosphoric oxide tube. The following observations were made:

1. At 80°: no appreciable reaction in twelve hours.
2. At 95°: 12 grams of benzamide (1 mol.) and 14 grams of benzoyl chloride (1 mol.) were heated at this temperature for eight hours.

Slow action occurred, and hydrogen chloride was slowly evolved. The latter, which was absorbed by passing into water, amounted to 1.88 grams. The reaction product in the flask contained, besides unchanged benzoyl chloride and benzamide, benzamide hydrochloride, small quantities of benzoic acid and benzonitrile, and 5 grams of dibenzamide, which, after crystallisation from aqueous alcohol, melted at 148°. (Found, N=6.56. Calc., N=6.30 per cent.)

3. At 125°: 12 grams of benzamide (1 mol.) and 52 grams (3 mols.) of benzoyl chloride were heated at this temperature for six hours, when the reaction was nearly complete. Two grams of hydrogen chloride were evolved, and from the liquid reaction product 3.7 grams of dibenzamide, which mostly crystallised out, were obtained. Large quantities of benzoic acid and benzonitrile were also obtained.

4. At 145°: 12 grams of benzamide (1 mol.) and 21 grams of benzoyl chloride (1.5 mols.) were heated at this temperature for twenty hours. 3.45 Grams of hydrogen chloride were evolved. The reaction product contained 1.5 grams of dibenzamide, 11.5 grams of benzoic acid, and 9 grams of benzonitrile.

Benzoyl Chloride and p-Toluidamide.

Similar observations were made to those with benzamide on the influence of temperature on the course of the reaction, and attention

was chiefly directed to the nature and amount of the products obtained at 140° , after complete reaction, and disappearance of the benzoyl chloride.

The treatment was as follows. The reaction product, which became semi-solid on cooling, was treated with benzene, and the insoluble *p*-toluamide hydrochloride, $C_6H_4Me \cdot CO \cdot NH_2 \cdot HCl$, together with a little ammonium chloride, collected and washed. The benzene filtrate was shaken with 10 per cent. aqueous sodium hydroxide in order to remove the acids (benzoic and *p*-toluic) and benzo-*p*-toluamide, and the alkaline extract was acidified with hydrochloric acid without delay so as to avoid decomposition of the secondary amide. The precipitate, after washing, was digested with aqueous sodium hydrogen carbonate, and the insoluble benzo-*p*-toluamide collected. It was practically pure, and melted before recrystallising at 114° . (Found, $N=5.64$. Calc., $N=5.8$ per cent.) Its properties were identical with those described by Wheeler, Johnson, and McFarland (*J. Amer. Chem. Soc.*, 1903, **25**, 787). The mixed acids, present in the filtrate after treatment with sodium hydrogen carbonate, were recovered by acidification, and the proportion of benzoic to *p*-toluic acid in the mixture was ascertained in two experiments by analysis of the mixed silver salts. The above benzene solution, after being washed with alkali, was immediately dried by sodium sulphate and saturated with dry ammonia to remove any acyl chloride as amide, but, with the proportions of reacting substances used (shown in the table), it was found that there was no appreciable quantity of acyl chloride present. The benzene was removed by distillation, and the residue treated with light petroleum in order to separate *p*-toluamide, which remained insoluble. After distilling off the light petroleum from the filtrate, the residual oil was fractionated. The liquid distillate consisted of a mixture of *p*-toluonitrile (mainly) and benzonitrile, and its composition was arrived at in one case by an estimation of nitrogen. In one experiment, when three molecular proportions of *p*-toluamide to one of benzoyl chloride were employed, the distillate consisted of almost pure *p*-toluonitrile, and immediately solidified on cooling. The following table shows the yields obtained, corrected for any loss due to solubility, and expressed on the same weight (10 grams) of benzoyl chloride.

Ratio of mols. of <i>p</i> -tolu- amide to mols. of benzoyl chloride.	<i>p</i> -Tolu- amide.	Temp.	Time.	Benzoic acid.	<i>p</i> -Toluic acid.	Benzo- acid. <i>p</i> -tolu- amide.	<i>p</i> -Tolu- amide hydro- chloride and am- monium chloride.	<i>p</i> -Toluo- nitrile.	Benzo- nitrile.
1 : 1	9.7	120°	8 hrs.	7.1	1.3	0.84	trace	5.0	
1 : 1	10.0	130	12 "		2.25	4.0	—	1.0	
1 : 1	9.7	140	6 "		8.4	0.56	0.56	3.5	0.7
0.85 : 1	8.3	140	14 "		4.2	1.1	—	2.7	
1 : 1	10.0	140	14 "		4.3	2.4	—	—	
3 : 1	26.1	140	6 "	6.1	4.8	2.4	4.35	8.5	trace

Action of Hydrogen Chloride on p-Toluidamide and Benamide.

A slow stream of dry hydrogen chloride was passed into 4 grams of *p*-toluidamide at 140–150°, moisture being excluded. *p*-Toluidoyl chloride and *p*-toluidonitrile were slowly formed, and appeared as a liquid in the neck of the flask. After heating seven hours, the reaction product was examined by treating with benzene, when 2.3 grams of *p*-toluidamide hydrochloride and 0.5 gram of ammonium chloride remained. The benzene filtrate, after treating as described on p. 1877, yielded *p*-toluic acid (0.2 gram), *p*-toluidoyl chloride (0.25 gram), *p*-toluidonitrile (0.3 gram), and di-*p*-toluidamide (0.04 gram)—the latter melting at 155–156°, and being identical in properties with the compound described by Krafft and Karstens (*Ber.*, 1892, 25, 454).

From these figures, which are low owing to mechanical loss, it is clear that the *p*-toluidamide has been converted primarily into *p*-toluidoyl chloride, which, by subsequent action on *p*-toluidamide, has yielded the corresponding secondary amide, nitrile, and acid, these overlapping reactions occurring under the above conditions to the extent of about 30 per cent. of complete decomposition.

The ammonium chloride formed by elimination of ammonia was found itself to be without influence on the course of the reaction, although it was at first suspected catalytically to bring about decomposition of an amide into nitrile and acid. By heating 4 grams of *p*-toluidamide with 1 gram of ammonium chloride at 160–170° for six hours, it was shown that no decomposition of the amide had taken place.

Similar observations to the action of hydrogen chloride on *p*-toluidamide have been made in the case of benamide, which slowly decomposes at 140° in presence of gaseous hydrogen chloride, yielding, besides benamide hydrochloride and ammonium chloride, benzoyl chloride, benzoic acid, benzonitrile, and small quantities of dibenzamide, the yields being similar to those obtained in the case of *p*-toluidamide.

Action of Hydrogen Chloride on Dibenzamide.

Three grams of dibenzamide were heated for four and a-half hours at 145° to 150° in an atmosphere of hydrogen chloride. The solid (m. p. 148°) gradually liquefied as decomposition occurred. No benzoyl chloride was formed, but benzoic acid and benzonitrile were produced in quantity. From the mixture 1.6 grams of benzoic acid were isolated (calc. for complete decomposition 1.63 grams). Owing to the difficulty of preventing loss of benzonitrile its yield was not determined.

At 140° the decomposition was considerably slower, and proceeded to the extent of only 24 per cent. in four hours.

Benzoyl Chloride and Acetamide.

Benzoyl chloride and acetamide react slowly even in the cold, and very rapidly at 80° , the temperature at which the reaction was studied. As acetamide hydrochloride, $(\text{CH}_3\cdot\text{CO}\cdot\text{NH}_2)_2\cdot\text{HCl}$, is always formed, three molecular proportions of acetamide were usually taken for each molecular proportion of benzoyl chloride. At 80° a homogeneous liquid is formed, from which acetamide hydrochloride is rapidly deposited, the reaction being apparently complete in five minutes, and a yellow, semi-solid mass resulting. On treatment with benzene, the filtrate from the acetamide hydrochloride was shaken with 10 per cent. aqueous sodium hydroxide in order to isolate the acid (benzoic). The residual benzene solution, after removing the benzene, gave an oil, which, after heating on the water-bath to remove any unchanged benzoyl chloride and being subsequently treated with aqueous sodium carbonate, left benzoic anhydride, which crystallised on keeping. No ammonium chloride was formed. Acetonitrile, which is always produced, was identified in a separate experiment by direct distillation, after ten minutes' heating. The liquid, which did not pass over until the temperature was raised considerably, boiled at 80° , and possessed the usual properties of acetonitrile. The yield was slightly less than that required by theory owing to slight polymerisation.

The following table shows the proportions yielded when the time and ratios of benzoyl chloride to acetamide were varied (expressed on 4.21 grams of benzoyl chloride=1 mol.).

Temperature 80° .						
Acetamide.	Benzoyl chloride.	Time in minutes.	Acetamide hydrochloride, grams.	Benzoic acid, grams.	Benzoic anhydride, grams.	Aceto-nitrile, grams.
3 mols.	1 mol.	15	3.5	1.87	0.5	—
3 „	1 „	60	—	1.7	0.95	—
2 „	1 „	15	3.0	1.35	0.79	—
3 „	1 „	10	—	—	—	1.0
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These figures indicate that an increased yield of benzoic anhydride is obtained by longer heating or by relative increase in the amount of benzoyl chloride, and it thus appeared to arise secondarily from the action of the benzoyl chloride on the benzoic acid formed. This was confirmed by (i) heating benzoyl chloride and benzoic acid together at 80° for one hour, and (ii) heating a mixture of acetamide and benzoic acid with benzoyl chloride. In (i) molecular proportions were taken, and 4.21 grams of benzoyl chloride were found to yield 0.59 gram of benzoic anhydride. In (ii) two molecular proportions of acetamide, one of benzoic acid, and one of benzoyl chloride (4.21 grams) yielded 3.0 grams of benzoic anhydride. This high yield of benzoic anhydride, in comparison to the yields obtained above, shows that acetamide disturbs the equilibrium between benzoyl chloride and benzoic acid, yielding the anhydride by removing the hydrogen chloride. In order to make sure that the benzoic anhydride did not arise, as it conceivably might by decomposition, through water, of an imino-ester, $\text{CH}_3\cdot\text{C}(\text{OBz})\cdot\text{NH}$, experiments were instituted involving treatment of the reaction product without intervention of water.

4.21 Grams of benzoyl chloride and 5.31 grams of acetamide were heated for fifteen minutes at 80° , and the benzene filtrate from the acetamide hydrochloride was treated with light petroleum, which separated a yellow oil. The oil, on washing with light petroleum (b. p. $35\text{--}45^{\circ}$), partly solidified, yielding crystals of impure acetamide (m. p. $68\text{--}75^{\circ}$), which remained on treatment with pure ether; benzoic acid, together with a little benzoic anhydride (total 0.2 gram) being removed. The light petroleum solution and washings contained also only benzoic acid, with some benzoic anhydride (total 2.5 grams), besides a little benzoyl chloride. No evidence could be obtained of an imino-benzoate. Further, in another experiment the reaction product, after removing acetamide hydrochloride, and subsequently the benzene, was fractionated. Benzoic acid passed over in quantity between 228° and 280° , leaving a small amount of benzoic anhydride in the distilling flask.

Acetyl Chloride and Benzamide.

Acetyl chloride and benzamide react slowly at the boiling point of the mixture, yielding acetobenzamide in large quantity. A considerable excess over the theoretical quantity of acetyl chloride was used. Twenty grams of benzamide and 105 grams of acetyl chloride were heated to boiling in a reflux apparatus for sixteen hours, care being taken to exclude moisture. After distilling off the excess of acetyl chloride from a water-bath, a red oil remained,

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which deposited acetobenzamide as a yellow solid on cooling. The crude product weighed 23 grams (theory requires 27 grams), and after crystallising from dilute alcohol the pure compound was obtained in colourless needles, melting at 116—117°.

Small quantities of benzoic acid and benzoyl chloride were also produced in the reaction, but no appreciable quantity of benzonitrile. In one experiment, after heating 12 grams of benzamide and 40 grams of acetyl chloride for sixteen hours and subsequently distilling off the excess of acetyl chloride, the product was treated with 9 grams of aniline dissolved in pure ether, in order to ascertain whether any chloro-compound was present. Practically no reaction occurred, and the solid, which separated after washing with water, consisted of acetobenzamide (6·5 grams). The ethereal solution, on removing the ether, left a mixture of aniline and a further quantity of acetobenzamide, together with a small quantity of acetanilide and benzanilide. By shaking with a large volume of water and digesting the resulting solid with aqueous sodium hydroxide to remove acetobenzamide, acetanilide and benzanilide remained, which were separated by boiling with light petroleum. The insoluble benzanilide (0·2 gram), after crystallisation from aqueous acetone, melted at 160°, and a mixture of the substance with pure benzanilide melted at 160—161°. The appearance of benzanilide after treatment with aniline shows that a small quantity of benzoyl chloride is formed in the action of acetyl chloride on benzamide, but benzoylphenylacetamidine, $\text{CH}_3\cdot\text{C}(\text{NHPh})\cdot\text{N}\cdot\text{COPh}$, which was specially looked for was not present.

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