[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF BROOKLYN COLLEGE]

# The Acylation of Amides

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Reaction between an acid amide and the corresponding acid anhydride leads, on the one hand, to the imide and acid, and on the other, to the nitrile and acid. These reactions are reversible, a three-way equilibrium being achieved thermally at about 200°. The products may be accounted for by assuming O-acylation to occur yielding isoimidinium carboxylate, $RC(=NH_2^+)OCOR\ RCOO^-$, which undergoes either scission to nitrile or rearrangement to imide. The former process predominates in the absence of acid catalysts and, in particular, when a very small proportion of catalyst is added; the latter reaction is dominant in the presence of substantial amounts of acids.

Acid amides react with the corresponding acid anhydrides in two ways, forming imides and nitriles. When the acid anhydrides are replaced by acid chlorides, nitriles may be the exclusive nitrogenous product. In the presence of pyridine, a third mode of reaction has been noted with acid chlorides at low temperature, *i.e.*, the formation of tertiary amides.

A number of peculiarities have been reported in connection with these reactions. Refluxing acetamide in acetic anhydride gives a low yield of diacetamide (29%) together with considerable acetonitrile.[1] Addition of a small proportion of acetyl chloride is said to increase the yield of imide to 70%.[2] In other cases, however, acid chlorides have had a deleterious effect on the yield of imides.[3] Other investigators of the acetamide–acetic anhydride reaction have claimed that heating for 30 hours at 98° yields only nitrile and acid (83% conversion at equilibrium).[4] In the presence of pyridine, benzoyl chloride produces tribenzamide more rapidly from benzamide than from dibenzamide, indicating that dibenzamide is not an intermediate (or is not the only intermediate) in the reaction with benzamide.[5]

The present study sought to clarify these facts and to find a theoretical path to account for the varied phenomena. The propionamide–propionic anhydride system was chosen for extensive study because of the ease with which the imide may be separated from the amide. A few ancillary experiments with other amides were included.

**Results.**—It has now been found that with a high-boiling system such as benzamide–benzoic anhydride, equilibrium with 2.7% of imide and about 90% of nitrile is reached within an hour by simply refluxing. Conversely equilibrium is reached within an hour on refluxing a mixture of benzonitrile with two moles of benzoic acid. With a lower-boiling system such as propionamide–propionic anhydride, reaction occurs readily enough at reflux as shown by the gradual fall in the boiling point of the reaction mixture, but equilibrium is not attained. The yield of imide is about 25%. A mixture of propionitrile and propionic acid scarcely reacts under the same conditions but its reflux temperature is much lower.

When 0.1 mole of sulfuric acid is included in the propionamide–propionic anhydride reaction a stable reflux temperature is reached in 10 minutes under reflux and the yield of imide is 46%. At 100°, heating for an hour gives a yield of imide of 74%. The same result is obtained over a range of sulfuric acid concentrations. Reaction is less rapid with the propionitrile–propionic acid mixture in the presence of sulfuric acid and the yield of imide is inferior.

It thus appears that the reaction between nitrile and acid to form imide which has previously been considered purely thermal[6-8] is acid catalyzed and may be carried out at temperatures much below the 200° formerly employed. Part of the nitrile, however, appears to be lost by a side reaction with the catalyst.[9]

Reaction between imide and acid has previously been postulated.[1] A refluxing mixture of dipropionamide and propionic acid displays a rapid *rise* in boiling point followed by a slow fall. This may be interpreted as being due to an initial partial conversion of the imide and acid to the higher-boiling mixture of amide and anhydride followed by the slow conversion of the latter to nitrile and acid. This was confirmed by a qualitative test for anhydride and the isolation of propionitrile. The reaction is catalyzed by sulfuric acid.

As has been said, the uncatalyzed reaction between propionamide and propionic anhydride yields about 25% of imide. As increasing amounts of propionyl chloride are included in the reaction mixture the yield of imide first falls to 14%, regains its original value at about 0.025 molecular proportion of propionyl chloride and gradually rises to 73% with one molecular proportion of propionyl chloride. Since propionyl chloride reacts with the propionic acid present in the reaction mixture to form propionic anhydride and hydrogen chloride, the latter is probably the actual catalyst. When a mole of propionyl chloride is added to a mixture of one mole of propionitrile and two moles

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[1] W. Hentschel, *Ber.*, **23**, 2395 (1890). This investigator assumed the reverse reaction between diacetamide and acetic acid to account for the presence of acetamide in the product.

[2] J. B. Polya and T. M. Spotswood, *Rec. trav. chim.*, **67**, 927 (1948).

[3] P. Dunn, E. A. Parkes and J. B. Polya, *ibid.*, **71**, 676 (1952).

[4] R. Kremann, A. Zoff and V. Oswald, *Monatsh.*, **43**, 139 (1922). These authors reported no chemical examination of the reaction mixture but followed the progress of the reaction by the freezing point of the reaction mixture. Under their conditions, it has now been found, considerable imide is formed. Reversibility of the reaction at 98° also was claimed, but this too could not be confirmed since a mixture of acetic acid and acetonitrile gave no test for acetic anhydride after heating for 48 hours on the steam-cone.

[5] Q. E. Thompson, THIS JOURNAL, **73**, 5841 (1951).

[6] A. Gautier, *Compt. rend.*, **67**, 1235 (1868); *Ann. chim.*, **150**, 187 (1869).

[7] W. König, *J. prakt. Chem.*, [2] **69**, 1 (1904).

[8] P. Bergell and J. Feigl, *Z. physiol. Chem.*, **54**, 269 (1907).

[9] Compare A. W. Cobb and J. H. Walton, *J. Phys. Chem.*, **41**, 351 (1937), in the case of HCN + $H_2SO_4$.

of propionic acid there is an immediate evolution of hydrogen chloride on refluxing, but no significant amount of imide is produced after refluxing for seven hours.

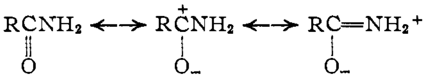
Ammonium halides also serve as catalysts for the formation of dipropionamide from propionamide and propionic anhydride. Ammonium iodide was the most active but was ineffective in the reverse reaction between propionitrile and propionic acid. Thus, no imide was obtained by a 5-hour refluxing of a propionitrile–propionic acid mixture with 0.1 mole of ammonium iodide.

As a consequence of the experiments described above it is now possible to control conditions so as to obtain high yields of either imide or nitrile in the reaction of amides with acid anhydrides. In this connection the striking case of the acetamide–benzoyl chloride and benzamide–acetyl chloride reactions is of interest.[10] The former has been reported to give exclusively acetonitrile and no imide, while the latter gives a high yield of imide and no nitrile. The hydrogen chloride present appears to be incapable of bringing these systems into equilibrium under the conditions employed. Nevertheless, hydrogen chloride has been found to bring about the reverse of the acetamide–acetyl chloride reaction when it was passed into a cold mixture of acetonitrile and acetic acid.[11]

The pyrolysis of imides must be expected to produce not only nitrile and acid as stated in the literature[12] but also amide and anhydride as required by the interlocking equilibria. The occurrence of an amide has been reported in the case of diacetamide[1] and the presence of anhydrides has been confirmed in the cases of diacetamide and dipropionamide in the present study.

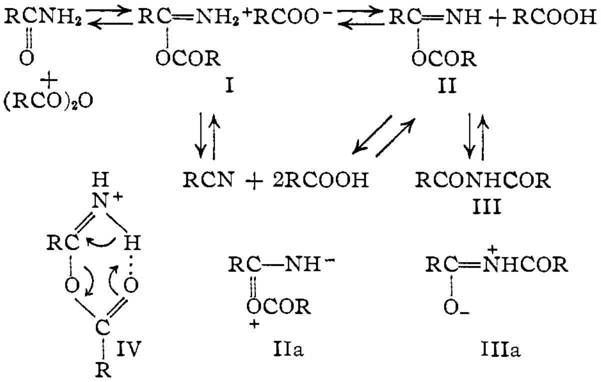
**Discussion.**—Since the uncatalyzed reaction of propionamide with propionic anhydride results in a high yield of propionitrile and since dipropionamide does not form propionitrile readily under the same conditions, it follows that the imide cannot be considered an intermediate in the formation of propionitrile. The following theory is offered to account for this and other peculiarities of the acylation of amides.

Amides may be represented as resonance hybrids of three structures.



$$\mathrm{R\underset{\underset{O}{\|}}{C}NH_2 \longleftrightarrow R\overset{+}{\underset{\underset{O_-}{|}}{C}}NH_2 \longleftrightarrow R\underset{\underset{O_-}{|}}{C}{=}NH_2^+}$$

From these it follows that the oxygen atom of the amide is partially anionic and the nitrogen atom partially cationic in character.[13,14] It may be expected, therefore, that electrophilic reagents will attack amides at the oxygen atom.[15-17] Hence the primary product of the attack of an anhydride on an amide may be the isoimidinium carboxylate (I). This can decompose into nitrile or rearrange into imide, the rate of decomposition being much greater than that of uncatalyzed rearrangement. The decomposition reaction is of the six-center type[18] and is not subject to catalysis. The rearrangement is an intramolecular acylation and may be particularly susceptible to acid catalysis.[19]



When an acid anhydride reacts with an amide the transitory base II may be assumed to enter into equilibrium with the corresponding carboxylate I. Enough of this base may be present to account for a moderate rate of rearrangement to imide III. A small amount of strong acid (0.002–0.010 equivalent) may serve to suppress this base without supplying sufficient acidity for acid catalysis of rearrangement (addition of a proton to the acyl group). This may explain the reduced yield of imide and consequent increased yield of nitrile obtained under these conditions. With a larger amount of strong acid, catalysis of acylation does occur and the yield of imide exceeds that obtained with the anhydride alone. The rearrangement of the isoimide II to the imide III is probably reversible as may be inferred from a consideration of the resonance structures IIa and IIIa.

Although the inclusion of a strong acid in the reaction mixture might be expected to decrease the concentration of the isoimide II and hence to retard the rearrangement reaction, quite the contrary occurs. This may be due to the great activation of the acyl group in the isoimidinium ion (in I) (by the addition of a proton to the carbonyl group), which more than compensates for the decreased con-

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[10] A. W. Titherley and T. H. Holden, *J. Chem. Soc.*, **101**, 1871 (1912).

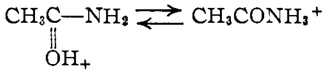
[11] A. Colson, *Bull. soc. chim. France*, [3] **17**, 55 (1897); *Ann. chim.*, [2] **12**, 250 (1897).

[12] C. D. Hurd and M. F. Dull, THIS JOURNAL, **54**, 2432 (1932).

[13] R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 1248 (1947).

[14] C. A. Grob and B. Fischer, *Helv. Chim. Acta*, **38**, 1794 (1955).

[15] L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, p. 193, calculated the basicity of the *nitrogen* atom of acetamide to be only one-millionth of that shown by the substance. This means that the equilibrium



$$\mathrm{CH_3\underset{\underset{OH_+}{\|}}{C}{-}NH_2 \rightleftarrows CH_3CONH_3^+}$$

has a constant of $10^{-6}$.

[16] Reference 9. These authors postulated O-benzoylation of acetamide by benzoyl chloride at 80° to account for the formation of acetonitrile and benzoic acid. They assumed the imidic acid, RC(OH)=NH, to be present. Such a structure has not been detected in amides and, theoretically, very little of such a tautomer could be in equilibrium with an amide because of their probable, wide difference in basicity and acidity.

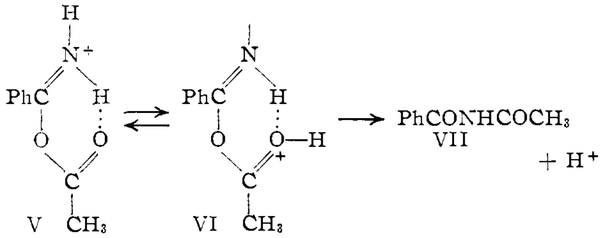
[17] D. Davidson and M. Karten, THIS JOURNAL, **78**, 1066 (1956), hypothesized O-acylation to occur in the uncatalyzed, self-acylation of amides which takes place at about 220°.

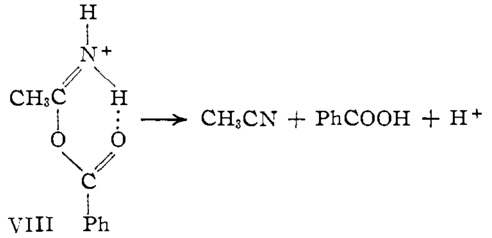
[18] J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 453.

[19] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 285.

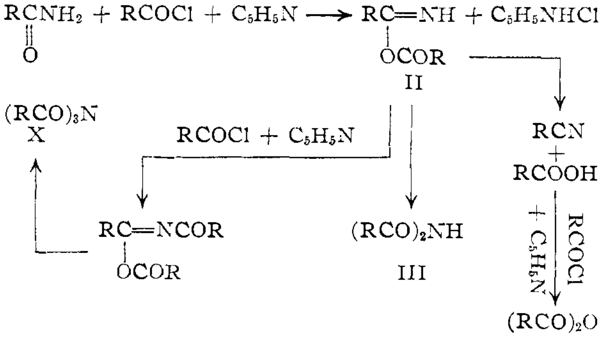
centration of the isoimide. An analogous situation occurs in the diazotization of primary aromatic amines where strong acid suppresses one reacting species (the amine) while increasing the other (the reactive nitroso-bearing species).

The opposed behavior of the acetamide–benzoyl chloride and benzamide–acetyl chloride mixtures mentioned above may be explained by considering the isoimidinium ions V and VIII. In V, the inductive effects of the phenyl and methyl groups promote proton transfer to form VI which readily rearranges to VII because of its ternary nitrogen atom and activated carbonyl group. In VIII, the interchange of the phenyl and methyl groups results in inhibiting the proton transfer sufficiently to allow the six-center reaction (formation of nitrile and acid) to predominate.





In pyridine-containing media, the reaction of amides with acid chlorides yields another species—the tertiary amide, $(RCO)_3N$—in addition to imide and nitrile and yields this so fast that its formation cannot be accounted for by an imide intermediate; that is, the two acyl groups introduced appear to enter the amide simultaneously.[5] The course of this reaction may be explained as follows. The process of O-acylation of the amide yields the isoimide II which, under these conditions, undergoes not only scission and rearrangement but also N-acylation to the N-acylisoimide IX. The latter, in turn, undergoes rearrangement to the tertiary amide X. Since the isoimide II would be a stronger base than the original amide[20] it follows that its acylation might be faster than the acylation of the amide and, hence, that the two acyl groups would appear to enter the amide together.[21,22] The isoimide, it should be noted, has a partially anionic nitrogen atom (IIa) and a partially cationic oxygen atom so that N-acylation is the reaction to be expected from it.



## Experimental[23]

1. **Thermal Reactions Leading to Equilibrium. A. Benzamide–Benzoic Anhydride.**—A mixture of 2.4 g. (0.020 mole) of benzamide and 4.5 g. (0.020 mole) of benzoic anhydride was refluxed gently in an inclined 8 × 1″ test-tube fitted with a vented cork bearing a thermometer leading to the bottom of the test tube. The highest temperature (243°) occurred at the beginning of the boiling, after which the temperature fell rapidly, leveling off at 224° after an hour. No further change occurred during another half-hour heating. After cooling, 10 ml. of benzene and 40 ml. of *M* sodium carbonate were added, the mixture shaken well, separated, and the benzene layer shaken again with 10 ml. of the carbonate solution. Acidification of the carbonate waters with concentrated hydrochloric acid gave 4.4 g. (0.036 mole) of benzoic acid, m. 118°. The benzene layer was then washed with five ml. of ice-cold 2 *M* sodium hydroxide and the alkali layer acidified with ice-cold hydrochloric acid. This yielded 0.12 g. (0.0054 mole, 2.7%) of dibenzamide, m. 146°. No further dibenzamide was yielded by a second extraction. Since a mole of benzoic acid was formed for each mole of dibenzamide, the benzoic acid resulting from the formation of benzonitrile (dehydration of the amide) was *at least* 0.0355 mole or 89%. Hence the residual benzoic anhydride was less than 8%. Titration of the residual oil layer with 0.1 *M* potassium hydroxide in methanol (after washing with water, evaporating in vacuum at room temperature and adding 10 ml. of methanol and thymol blue) indicated 0.00090 mole or 4.5% of benzoic anhydride.

**B. Benzonitrile–Benzoic Acid.**—A mixture of 2.06 g. (0.020 mole) of benzonitrile and 4.9 g. (0.040 mole) of benzoic acid was refluxed as described above. The boiling began at 219° and gradually rose to 224° within an hour. After a total of two hours heating the mixture was worked up as before and yielded 2.7% of dibenzamide and a titration corresponding to 4.6% of benzoic anhydride.

Similar experiments with other systems gave the following results on approaching equilibrium from the nitrile-acid side. The phenylacetic acid system leveled off in 15 minutes (250–257°) and after 30 minutes showed 17% of imide (m. 193°) and 6.7% of anhydride. In this case the imide crystallized out in large part during the carbonate washing. In the caproic acid system equilibrium was reached in four hours (183–188°) with 9.4% of imide and 2.0% of anhydride. Here, the imide could not be extracted from the benzene solution by means of sodium hydroxide. It crystallized, however, on removal of the benzene and the addition of petroleum ether. It melted at 93° and gave the characteristic tests for imides (A-I indicator reagent and hydroxamic acid[17]).

2. **Propionamide–Propionic Anhydride. A. At Reflux.**—A mixture of 3.7 g. (0.050 mole) of propionamide and 7.1 g. (0.055 mole) of propionic anhydride was refluxed for a given time in an inclined 50-ml. Claisen flask bearing a thermometer reaching into the bulb in the main tube and a cold-finger condenser in the side tube. Boiling began at 166° and the temperature fell rapidly, ultimately to 131°. After cooling, 25 ml. of ice-water was added and the product

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[20] The $pK_b$'s of the closely related imido esters range from 8–9 (R. B. Hartigan and J. B. Cloke, THIS JOURNAL, **67**, 709 (1945)).

[21] Q. E. Thompson[5] found that ammonia does not undergo "diacylation," although water and hydrogen sulfide appear to do so. Ammonia, of course, is a stronger base than its monoacyl derivative, the amide, and hence *it* is acylated rather than the amide. In the case of water and hydrogen sulfide, the phenomena may be explained as follows. When one-half a mole of water is gradually added to a solution of an acid chloride in pyridine very little carboxylic acid is present at any given moment so that there is little effect on the basicity of the medium from this source. When the acid, itself, is added, however, there is a marked decrease in the basicity of the medium and, hence, in the rate of acylation.

[22] K. Brunner, *Ber.*, **47**, 2671 (1914).

[23] Three-inch immersion thermometers were employed. The temperatures reported may be considered corrected.

filtered. Dipropionamide was identified by its m.p. (154°) and by its qualitative behavior.[17] The effect of time of heating (in hours) on the percentage yield of dipropionamide follows: 0.5, 16; 1, 20; 2, 23; 3, 23; 4, 23.

**B. With Fractional Distillation.**—A mixture of 36.5 g. (0.50 mole) of propionamide and 71 g. (0.55 mole) of propionic anhydride was distilled slowly (three hours) in a 125-ml. modified Claisen flask having an 8″ Vigreux column and bearing one thermometer reaching into the bulb and one in the side-arm. The rate of distillation was controlled so that the side-arm thermometer remained between 105 and 110°. Under these conditions the temperature of the boiling liquid fell from 156–149° and then rose again to 155°. The distillate consisted of 20 g. (72%) of propionitrile, while the residue yielded 17.2 g. (27%) of dipropionamide, m. 154°, on treatment with ice-water.

**C. At 100°.**—When experiment A was repeated using heating on the steam-bath for 48 hours, the yield of dipropionamide was 16%.

**D. Sulfuric Acid Catalysis at Reflux.**—When experiment A was repeated with the inclusion of 0.0050 mole (0.10 molecular proportion) of 100% sulfuric acid the yield of dipropionamide was 46%. The same result was obtained in heating periods of 10 and 90 minutes.

**E. Sulfuric Acid Catalysis at 100°.**—When experiment D was repeated but with heating at 100° for one hour the yield of imide was 74%. The same yield was obtained when a smaller amount of sulfuric acid was used (0.032 molecular proportion) and the heating extended for seven hours. With larger amounts of catalyst and one-hour heating the yield fell. Thus 0.32 mole of sulfuric acid gave a 68% yield and 1.0 mole gave a 16% yield.

**F. Propionyl Chloride Catalysis at Reflux.**—When experiment A was repeated with the inclusion of varying amounts of propionyl chloride the results given in Table I were obtained. The heating was continued for one hour after the reflux temperature had leveled off.

TABLE I

YIELDS OF DIPROPIONAMIDE FROM PROPIONAMIDE AND 1.1 MOLES OF PROPIONIC ANHYDRIDE IN THE PRESENCE OF VARIOUS AMOUNTS OF PROPIONYL CHLORIDE

| Equiv. EtCOCl | Yield of $(EtCO)_2$-NH, % | Behavior on refluxing | Temp. range, °C. |
|---|---|---|---|
| 0.000 | 25 | Levels in 10 hr. | 166–131 |
| .002[a] | 14 | Levels in 2 hr. | 153–130 |
| .005 | 14 | Levels in 2 hr. | 150–130 |
| .009 | 14 | Levels in 2 hr. | 145–131 |
| .025 | 25 | Levels in 1.5 hr. | 150–133 |
| .05 | 33 | Levels in 0.5 hr. | 151–133 |
| .10 | 42 | Falls for 10′, levels in 0.5 hr. | 145–136–137 |
| .20 | 53 | Falls for 5′, levels in 50′ | 140–136–140 |
| .40 | 64 | Falls for 2′, levels in 25′ | 139–133–143 |
| 1.00 | 73 | Falls for 2′, levels in 30′ | 117–115–138 |

[a] An equimolecular quantity of sulfuric acid gave the same result.

**G. Catalysis by Ammonium Salts.**—Modification of experiment A by the inclusion of a 0.1 molar proportion of ammonium salts gave the following results: chloride, 30 min., 26%; 90 min., 39%; bromide, 10 min., 54%; 30 min., 53%; 90 min., 48%; iodide, 30 min., 59%; sulfate, 30 min., 34%; primary phosphate, 30 min., 11%. Of these salts only the iodide dissolved completely in the reaction mixture.

**H. Propionitrile-Propionic Acid.**—Refluxing of a mixture of propionitrile with two molecular proportions of propionic acid for 200 hours yielded less than 1% of dipropionamide. No improvement occurred when 0.1 molecular proportion of propionic anhydride was included to assure anhydrous conditions. The further inclusion of a 0.1 molecular proportion of sulfuric acid, however, gave a reaction mixture which leveled off in three hours (121–141°) and gave a 28% yield of dipropionamide. This reaction mixture gave no yield after two hours on the steam-bath; however, with 0.32 molecular proportion of sulfuric acid, two hours on the steam-bath gave 22% of dipropionamide; with one molecular proportion of sulfuric acid, the yield fell to 9% under these conditions and with two molecular proportions to zero. No imide was obtained in refluxing similar reaction mixtures in which the sulfuric acid was replaced by 0.1 molar proportion of ammonium iodide or of trimethylammonium chloride or even in the case of one molecular proportion of the latter salt (three hours). A molar proportion of propionyl chloride was also ineffective.

**I. Dipropionamide-Propionic Acid.**—A mixture of 6.5 g. (0.050 mole) of dipropionamide and 3.7 g. (0.050 mole) of propionic acid was refluxed as described in A. The refluxing temperature was initially 167°. In ten minutes it rose to 174° where it remained for an hour and then began a slow decline to 150° in the course of 80 hours. Distillation gave 1.4 g. of distillate boiling below 140° from which water and solid potassium carbonate yielded 0.4 ml. of oil (propionitrile). A 48% recovery of dipropionamide was obtained from the residue by adding 25 ml. of ice-water. In a separate experiment a qualitative test for anhydride[24] was given after refluxing for ten minutes. When the reaction mixture (32.3 g. of imide and 18.5 g. of acid) was modified by the inclusion of sulfuric acid (0.10 molecular proportion) the reflux temperature did not pass through a maximum and leveled off in two hours (161–154°). Fractionation gave a 41% yield of propionitrile and 13% of imide was recovered on adding ice-water to the residue.

**3. A. Acetamide–Acetic Anhydride at 100°.**—A mixture of 5.9 g. (0.10 mole) of acetamide and 11.0 g. (0.11 mole) of acetic anhydride was heated on the steam-bath for 48 hours. Volatile products (acetonitrile, acetic acid and acetic anhydride) were removed by distillation from a water-bath at 10 mm. The residue weighed 3.7 g., crystallized slowly at room temperature (a peculiarity of acetamide–diacetamide mixtures), melted at 62°, and gave the characteristic tests for imides.[17]

**B. Acetonitrile–Acetic Acid at 100°.**—A mixture of 4.1 g. (0.10 mole) of acetonitrile and 12.0 g. (0.20 mole) of acetic acid was heated for 48 hours on the steam-bath. The cooled liquid gave no test for anhydride directly or after removal of $^7/_8$ of the material by distillation. It left no residue on distillation from a water-bath at 10 mm.

**4. The Occurrence of Anhydrides in the Pyrolysis of Imides.**—When boiled under reflux for three minutes and then cooled, 0.3 g. of diacetamide gave a conspicuous test for anhydride.[24] Dipropionamide behaved similarly.

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[24] D. Davidson, *Anal. Chem.*, **26**, 576 (1954).