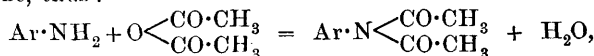


# CXIX.—*Acids as Accelerators in the Acetylation of Amino-groups.*

By ALICE EMILY SMITH and KENNEDY JOSEPH PREVITÉ ORTON.

DI-*o*-SUBSTITUTED anilines are notoriously difficult to monoacetylate by means of acetic anhydride if the two ortho-placed atoms or groups are of negative character. Remmers (*Ber.*, 1874, **7**, 350), who investigated systematically the effect of the constitution of the aniline on the rapidity and readiness of acetylation, ascertained that of negative substituents the nitro-group more effectually prevents acetylation than the halogens. Boiling or heating these anilines under pressure with acetic anhydride leads to the formation of a di-, but not of a mono-acetyl derivative (Remmers, *loc. cit.*; Ulffers and von Janson, *Ber.*, 1894, **27**, 93; Sudborough, *Trans.*, 1901, **79**, 532; Orton, *Trans.*, 1902, **81**, 495).

The rapid formation of the diacetyl derivative cannot, as has been suggested, be regarded as due to the direct action of the anhydride on the aniline, thus :



for the monoacetyl derivative is just as easily converted into the diacetyl compound as the aniline; moreover, in the treatment of the aniline with the anhydride, the monoacetyl derivative can always be recognised in the early stages of the acetylation. Sudborough's view that the readiness of diacetylation is conditioned by the stability of an acetate formed from the monoacetyl derivative and the acetic anhydride is not open to the same objection.

When the di-*o*-substituted aniline has two or more methyl (or alkyl) groups as substituents in the nucleus (xylenes,  $\psi$ -cumene, &c.), one of

which groups is in juxtaposition to the amino-group, acetylation is normal.

We have made the observation that the acetylation of such di-*o*-substituted anilines (for example, *s*-tribromoaniline) by acetic anhydride is enormously accelerated by strong acids. Hydrochloric, sulphuric, perchloric, and trichloroacetic acids have been used as catalysts. Nitric and chromic acids behave exceptionally, the former producing a nitroaminobenzene (Orton, *Trans.*, 1902, **81**, 490, 860), and the latter acting as an oxidising agent.\*

The effect of the acid as an accelerator is made obvious by the following experiment. A solution of one gram of *s*-tribromoaniline in 20 c.c. of acetic anhydride was kept for a fortnight at the ordinary temperature. The solid was then precipitated by addition of warm water; it melted at 119°, the melting point of the pure aniline. A similar solution was treated with two drops of concentrated sulphuric acid (about 1 gram-molecular proportion), the mixture being kept at the ordinary temperature; at the end of ten minutes, it was poured into warm water; the solid which separated melted at 231°, the melting point of *s*-tribromoacetanilide being 232° (corr.).

The acetylation also takes place, but not so rapidly, if the proportion of acetic anhydride is reduced and the mixture diluted with glacial acetic acid.†

*Experiment.*—One gram of *s*-tribromoaniline was dissolved in a mixture of 40 c.c. of glacial acetic acid and 4.5 c.c. (15 gram-molecular proportions) of acetic anhydride to which 0.16 c.c. (1 gram-molecular proportion) of sulphuric acid (96 per cent.) was added. The mixture was maintained at the ordinary temperature. At the end of ten minutes, 91 per cent., and at the end of twenty minutes 98–99 per cent., of the aniline was found to be acetylated. The composition of the mixture was determined by estimation of the bromine.‡

\* Since nitric acid and acetic anhydride convert the aniline into a nitroamine,  $\text{Ar}\cdot\text{NH}_2 + \text{HO}\cdot\text{NO}_2 = \text{Ar}\cdot\text{NH}\cdot\text{NO}_2 + \text{H}_2\text{O}$ , it might have been anticipated that anilides of sulphuric, for example,  $\text{Ar}\cdot\text{NH}\cdot\text{SO}_3\text{H}$ , or of perchloric acid,  $\text{Ar}\cdot\text{NH}\cdot\text{ClO}_3$ , would be produced. No indication of the presence of such substances was detected.

† The commercial acetic anhydride (puriss.) was found to contain traces of sulphate and chloride, which were removed by careful distillation. The acetic acid used by us was fractionated, and then melted at 16.1°. Hence it contained 0.3 per cent. of water.

‡ When in a mixture of *s*-tribromoaniline and *s*-tribromoacetanilide both substances are present in considerable proportion, separation is exceedingly difficult to bring about by recrystallisation from the usual solvents. It is possible, however, to extract the anilide from the mixture by addition of 10 per cent. of sodium hydroxide to a suspension of the solid in alcohol. The anilide entirely dissolves, and, if the liquid is sufficiently diluted with water, no aniline remains in solution in the dilute alcohol. If any diacetyl derivative, which is, of course, insoluble in the alkali, be present, it remains mixed with the aniline (compare Orton, *Trans.*, 1902, **81**, 495.)

Inasmuch as acetic anhydride is without action on *s*-tribromoaniline at the ordinary temperature and yet at the boiling point converts the aniline into the diacetyl derivative, trials have been made with acetic anhydride at temperatures varying between 70° and 100°, and with mixtures of acetic acid and anhydride at these temperatures and at their boiling point. In all cases, a slow acetylation took place.

*Experiment.*—(1) A solution of 1 gram of the aniline in 20 c.c. of the anhydride was heated at 75°; after two hours, the product contained 25 to 30 per cent. of anilide. More prolonged heating showed that conversion of the mono- into the di-acetyl derivative followed hard on the formation of the former; the melting point of the product rose to a maximum at 192° in three hours, and then gradually fell until the melting point of the pure diacetyl derivative (125°) was reached (see p. 1246).

(2) A solution of 1 gram of the aniline in a mixture of 15 c.c. of acetic anhydride and 20 c.c. of acetic acid was boiled in a reflux apparatus. After six and a-half hours, some 50 per cent. of the aniline was converted into the monoacetyl derivative; after forty-eight hours, the transformation was complete; after ninety-six hours' boiling, no further change, namely, that of the mono- into the di-acetyl derivative, was detected.

Other anilines with like substituents, for example, 2:6-dibromo-4-nitro- and 2:4-dibromo-6-nitro anilines, behave generally in the same way as 2:4:6-tribromoaniline. They are not only acetylated by acetic anhydride extremely slowly at 100°, but are converted in some cases with even greater readiness than the *s*-tribromoaniline into diacetyl derivatives when boiled with this reagent. In the presence of mineral acids, they form monoacetyl derivatives with great rapidity.

The result is very different when anilines of other constitution are treated in the manner described in the foregoing. The acetylation of an aniline in which only one ortho-position is occupied by a negative group is an extremely rapid process. When, for example, a solution of 0.5 gram of 2:4-dibromoaniline in 45 c.c. of glacial acetic acid to which 1.25 c.c. ( $6\frac{1}{4}$  gram-molecular proportions) of acetic anhydride was added, was kept for five minutes at the ordinary temperature and then poured into boiling water, a quantitative yield of the corresponding anilide (m. p. 144°) was obtained. The addition of mineral acid depresses the speed of acetylation.

Thus, on addition of 2-gram-molecular proportions of hydrochloric acid to the mixture, the presence of the anilide in the product can only just be detected (by fractional precipitation of the solution by water) at the end of five minutes; in an hour, however, acetylation was complete.

A series of experiments on the acetylation of aniline demonstrate the inhibiting effect of acid on the speed of acetylation.

Aniline.	Glacial acetic acid.	Acetic anhydride.	Sulphuric acid.	Anilide.	Percentage of aniline acetylated.
A. 1 gram	20 c.c.	10 c.c. (9 gr.-mol.)	0	1.34 gr.	92
B. „	„	„	1 gr.-mol.	1.25 „	85.7
C. „	„	3.3 c.c. (3 gr.-mol.)	0	1.29 „	88.6
D. „	„	„	1 gr.-mol.	0.43 „	29.5

The four mixtures were kept for one and a-half hours at  $10^{\circ}$ , then poured into 35 c.c. of warm water, and the liquid, which was placed in a shallow glass dish, was evaporated at the ordinary temperature by drawing rapidly over it a current of air. The anilide, which separated in large crystals, was collected and weighed. In experiment *A*, the acetylation of the aniline, which was shown in other experiments to be complete in a few minutes, was probably quantitative, the solubility of the anilide in the dilute acetic acid accounting for the deficiency of 8 per cent. A comparison of *A* with *B*, and *C* with *D*, brings out very clearly the reduction of the rate of acetylation by the mineral acid.

*Effect of the Nature of the Acid.*—In testing the effect of acids other than sulphuric, difficulties arise, on the one hand, owing to the low solubility of the acid in the acetic acid or anhydride, and, on the other, in the preparation of the acids in a highly concentrated form. Nitric and chromic acids, which offer less difficulty in these respects, behave, as previously stated, exceptionally; the acceleration of acetylation is masked by other reactions, although traces of the acetyl derivative can be detected with each acid.

We have been able, however, to demonstrate satisfactorily the accelerating effect of hydrochloric, perchloric, and trichloroacetic acids.

A solution of 0.5 gram of *s*-tribromoaniline in 10 c.c. of acetic anhydride to which was added 0.15 c.c. of a 37 per cent. solution of hydrochloric acid (1 gram-molecular proportion) was kept for one and a-half hours, and then poured into warm water. *s*-Tribromoacetanilide, which separated, melted at  $227\text{--}229^{\circ}$ , instead of at  $232^{\circ}$ . As hydrochloric acid is all but insoluble in acetic anhydride, the concentration of the acid, owing to its obvious escape from the solution, must have fallen below the initial value.

Experiments carried out in acetic acid solution, in which hydrochloric acid is somewhat more soluble, led to a similar result. The aniline and anhydride were in the molecular ratio of 1:15, 2 gram-molecules of the hydrochloric acid being present.

Perchloric acid was used in the form of a 5*N*-solution. In one

experiment, one gram of *s*-tribromoaniline dissolved in 38 c.c. of acetic acid (98 per cent.) was treated with 5.45 c.c. (18.2 gram-molecular proportions) of acetic anhydride and 0.6 c.c. (1 gram-molecular proportion) of 5*N* (50.25 per cent.) perchloric acid. The mixture was kept for half an hour at the ordinary temperature, and then poured into warm water. The solid material thus obtained, which was a mixture of *s*-tribromoaniline and -acetanilide, contained 50 per cent. of the latter.

Trichloroacetic acid accelerated the acetylation, but in a far less pronounced manner than the other acids which were tested. In an experiment similar to that just described, only 20 per cent. of the anilide was produced after twenty hours at the ordinary temperature.

#### *Formation of Diacetylanilides.*

The formation of diacetyl derivatives is aided by the presence of an acid, but in nothing like the same degree as that of the monoacetyl derivatives.

A solution of 0.2 gram of *s*-tribromoaniline in 20 c.c. of acetic anhydride, to which 0.25 gram-molecular proportion of sulphuric acid was added, contained only the monoacetyl derivative after ten minutes. After remaining for three hours at the ordinary temperature, the formation of the diacetanilide was distinctly shown by the depression of the melting point from 231° (the melting point of the monoacetyl derivative) to 192—213°, but only after forty-eight hours was the diacetylation complete.

If, on the other hand, this mixture, containing the monoacetyl derivative and the sulphuric acid, was maintained at 70—80°, instead of at the ordinary temperature, a quantitative conversion into the diacetyl derivative was brought about in one hour. That the elevation of temperature alone is not the cause of this rapid production of the diacetyl derivative is shown by the fact that only after seven hours' heating of a solution of the monoacetanilide in acetic anhydride at 70—80° is some 70 per cent. of the diacetanilide formed.

At the ordinary temperature, no change was detected in a solution of the acetanilide in acetic anhydride after a long period. The mixture of acetic anhydride and acetic acid used by us (p. 1249), as the experiments described in the foregoing demonstrate, will not carry the acetylation further than the formation of the monoacetyl derivative.

The speed of diacetylation is markedly dependent on the constitution of the aniline. For example, when a nitro-group replaces the para-placed bromine atom, as in 2:6-dibromo-4-nitroaniline, monoacetylation in acetic anhydride solution is complete in five minutes in the presence of a quarter or even one-thirteenth gram-molecular pro-

portion of sulphuric acid. This is all the more remarkable, as the solubility of this aniline is such that on using 20 c.c. of anhydride for 0.5 gram of aniline, the major part of the base remains in suspension. If the aniline is sufficiently finely divided, it dissolves very rapidly, the anilide partly separating. When the larger proportion of sulphuric acid is used, the formation of the diacetyl derivative follows quickly on that of the monoacetyl compound. In half an hour, the melting point of the solid product falls far below that of the acetanilide, and after two hours is that of the pure diacetyl derivative.

### *Acetylation of Phenols.*

According to Skraup (*Monatsh.*, 1898, **19**, 458), the acceleration of acetylation of hydroxy-groups by sulphuric acid appears to have been first observed and put into practice in the acetylation of cellulose, &c., by Franchimont (*Compt. rend.*, 1879, **89**, 711). This chemist used the acid as an alternative to zinc chloride and similar reagents, and seemed to regard it as a dehydrating agent. This view, however, is untenable in the light of Skraup's results. The latter ascertained that mere traces of sulphuric acid had a very powerful effect on the acetylation of various hydroxy-compounds by acetic anhydride. Later, Freyss (*Bull. Soc. Ind. Mulhouse*, 1899, 44) tested the use of sulphuric acid in the acetylation of phenols, aldehydes, and amino-phenols, &c. Thiele's preparation (*Ber.*, 1898, **31**, 1249) of acetyl derivatives of quinols by treatment of the corresponding quinones with acetic anhydride and sulphuric acid can scarcely be regarded as a reaction of the same type.

To test the effect of different acids, we have chosen *s*-tribromophenol, which yields an acetyl derivative (m. p. 82°), easily isolated and weighed. In the presence of 0.25 gram-molecular proportion of sulphuric acid, a solution of the phenol in a mixture of acetic acid and acetic anhydride (50 per cent.), kept at the ordinary temperature, contains only acetate after half an hour. On replacing the sulphuric acid by perchloric acid, acetylation is equally rapid. In the absence of acid, the phenol is unchanged after twenty-four hours. Nitric acid reacts with the phenol, bromine being eliminated, whilst hydrochloric and trichloroacetic acids scarcely produce an appreciable effect.

### *Part Played by the Acid.*

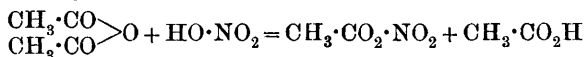
In our experiments, we have demonstrated that many acids, not only sulphuric acid, are accelerators of acetylation.\* For this effect to

\* In D.R.-P. 147033, a method of acetylating phenylglycine-*o*-carboxylic acid by saturating a solution in acetic anhydride with dry hydrogen chloride is described. The reaction appears to be ascribed to the formation of acetyl chloride.

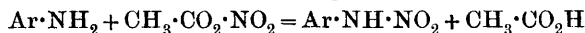
appear in the case of amines, our results show it to be essential that the amino-group should possess very little power of combining with acids to form ammonium salts. The speed of acetylation of the more basic anilines is lowered, not raised, by acids. When the amino-group is between two ortho-placed (negative) groups, its combining power with acids is, as is well known, greatly reduced, partly possibly on account of the negative character of these groups, and partly by virtue of a steric effect. Moreover, such an amino-group reacts very tardily with acetylating agents, such as acetic anhydride or acetyl chloride. Hence the specific accelerating action of the acid has an opportunity of making itself felt, and is no longer masked either by the conversion of the amino-group into the ammonium compound, which at the same time removes the acid, or by the too rapid action of the amino-group with the acetic anhydride.

It is not easy at present to state with precision what is the part played by the acid. Thiele and Winter (*Annalen*, 1900, **311**, 341) are of the opinion that in the acetylation of hydroxy-groups, an anhydride of sulphuric acid and acetic acid,  $\text{CH}_3\cdot\text{CO}\cdot\text{O}\cdot\text{SO}_3\text{H}$ , is first formed, which then reacts with the hydroxy-group. This substance was thought by Franchimont to be present in solutions of sulphuric acid in acetic anhydride, and to become converted into a sulphonic derivative of acetic acid, which he isolated.

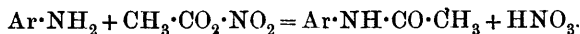
The peculiar behaviour of nitric acid may be accounted for in this way. The anhydride formed thus :



might react with the aniline according to one of the equations :



or



As a fact, the acetanilide forms a very small fraction of the product, whereas in the case of sulphuric acid the reaction is mainly, if not entirely,  $\text{Ar}\cdot\text{NH}_2 + \text{CH}_3\cdot\text{CO}_2\cdot\text{SO}_3\text{H} = \text{Ar}\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_3 + \text{H}_2\text{SO}_4$ . The feeble effect of hydrochloric acid may also be due to a reluctance to form an anhydride, which is in this case acetyl chloride.

If the cause of the acceleration is to be found in a union of the acid and anhydride, it may be suggested that the complex is not a definite anhydride, but rather of the nature of an oxonium salt,  $\begin{array}{c} \text{CH}_3\cdot\text{CO} \\ \text{CH}_3\cdot\text{CO} \end{array} \text{O} \begin{array}{c} \text{H} \\ \text{X} \end{array}$ .

On such a view less difference would be expected between the various acids than on the hypothesis that the formation of an anhydride is the first step.

The presence of an acid has another effect, which probably plays an important part when the acetylation is carried out in acetic acid

solution, that is, in greatly accelerating the interaction of water and the anhydride. In this way, the small quantities of water present in the acetic acid, or in the acid added as catalyst, are removed, and hence the reverse reaction, the hydrolysis of the anilide, is rendered impossible.

The effect of variation of the proportion of the acid on the rate of acetylation of amines and phenols, and a study of the dynamics of the reaction, are under investigation. The preliminary experiments indicate that the speed of acetylation is proportional to the square of the concentration of the acid, that is, doubling the concentration of the acid quadruples the velocity.

*Preparation of the Monoacetyl Derivatives of Di-ortho-substituted Anilines.*

Most anilines with two negative groups, such as the halogens and the nitro-group, in the ortho-position with respect to the amino-group can be quantitatively converted into their monoacetyl derivatives by the following procedure.

One gram of the aniline is dissolved in 40 c.c. of glacial acetic acid (98—100 per cent.), or in some cases when the aniline is very insoluble it is suspended in this quantity of solvent. Acetic anhydride is next added to the mixture; we have generally used 15 gram-molecular proportions of acetic anhydride to one gram-molecular proportion of aniline, that is, from about 4—6 c.c. of acetic anhydride for one gram of aniline, according to the molecular weight of the aniline. 0.08 c.c. (about four drops) of concentrated sulphuric acid is then introduced, and the mixture kept at the ordinary temperature for forty minutes to an hour. It is then poured into 100 c.c. of warm water, whereupon the anilide immediately separates. Increase of the acetic anhydride hastens the acetylation, but there is danger in some cases, if too large an excess of acetic anhydride is present, of the production of the diacetyl derivative.

We have found this method well adapted to the preparation of the monoacetyl derivatives of 2:4:6-tribromoaniline and other similar *s*-trihalogen anilines, for 2:6-dichloro- and 2:6-dibromo-4-nitroanilines, for 2:4-dichloro-6-nitroaniline, and for 3-bromo-5-nitro-*p*-toluidine.

2:6-Dibromoaniline appears to be somewhat exceptional, and is acetylated only if the proportion of anhydride is considerably higher than that given above. We have prepared the monoacetyl derivative by dissolving the aniline in acetic anhydride and adding the usual proportion of sulphuric acid. The acetylation was complete in two hours.



*Preparation of Diacetyl Derivatives.*

The di-*o*-substituted anilines just mentioned all form diacetyl derivatives with ease in the presence of mineral acid when the mixture of aniline and acetic anhydride is not diluted with acetic acid, but the rapidity of the reaction depends considerably on the constitution of the aniline. For example, 2 : 6-dibromo-*p*-nitroaniline yields a diacetyl derivative more readily than *s*-tribromoaniline.

*s*-**Tribromodiacetanilide**.—This compound can be easily prepared in the following manner: 1 gram of *s*-tribromoaniline is dissolved in 40 c.c. of acetic anhydride to which 0.08 c.c. sulphuric acid ( $\frac{1}{2}$  gram-molecular proportion) has been added. The mixture is placed on the water-bath (70—80°) for one hour, and then poured into 100 c.c. of warm water, whereupon the diacetyl derivative crystallises out in the pure state.

2 : 6-**Dichloro-4-nitroacetanilide**.—One gram of the aniline is suspended in 40 c.c. of acetic anhydride to which 0.08 c.c. of sulphuric acid has been added. The aniline passes into solution, the colour disappearing very rapidly. After remaining for two hours at the ordinary temperature, the mixture is poured into warm water. The diacetanilide separates directly in a nearly pure state, melting at 138° instead of 140°.

*The Acetylation of Heptabromo-p-hydroxydiphenylamine (s-Tribromophenyl-2' : 3' : 5' : 6'-tetrabromo-4-hydroxyphenylamine).*

In our investigation of the hydroxydiphenylamines (this vol., p. 314), we were unable to prepare the acetyl derivatives by heating the compounds with acetic anhydride and sodium acetate in the ordinary way. We find, however, that the monoacetyl derivatives, in which the acetyl group has replaced the hydrogen of the hydroxy-group, can be very easily obtained when a trace of sulphuric acid is added to the anhydride instead of the sodium acetate.

0.5 Gram of heptabromohydroxydiphenylamine is suspended in 50 c.c. of acetic anhydride to which 0.1 c.c. of sulphuric acid has been added. The mixture is warmed for fifteen minutes on the water-bath, when the compound completely dissolves. On cooling, the *acetate* separates in small, colourless, granular crystals, melting at 193°. The insolubility in warm alcoholic sodium hydroxide showed that the compound no longer contains a hydroxyl group :

0.1212 gave 0.2043 AgBr. Br = 71.74.

$C_{14}H_6O_2NBr_7$  requires Br = 71.78 per cent.

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