LVIII.—*Acetylation of Arylamines.*

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IN the preceding communication (p. 528), it has been shown that when α -naphthylamine trinitrobenzene is warmed for a few minutes with an excess of acetic anhydride, a monoacetyl derivative, $C_6H_3(NO_2)_3 \cdot C_{10}H_7 \cdot NHAc$, is formed, but that when the heating is prolonged for an hour decomposition ensues, and the products are trinitrobenzene and diacetyl- α -naphthylamine. This result pointed to the remarkable readiness with which α -naphthylamine or its monoacetyl compound is converted into a diacetyl derivative, and it was considered advisable to try a few comparative experiments with α - and β -naphthylamines.

Some few years ago, Kay (*Ber.*, 1893, 26, 2851) showed that diacetyl derivatives of aniline and *o*- and *p*-toluidine can be obtained

by the action of acetyl chloride on the monoacetyl compounds at a temperature of 180° . The following year, Bistrzyki and Ulffers (*Ber.*, 1894, 27, 91) showed that acetic anhydride could be substituted for the chloride, and that if the temperature be raised to $200-205^{\circ}$, a 90 per cent. yield of the diacetyl compound may be obtained. About the same time, Ulffers and von Janson (*Ber.*, 1894, 27, 93) investigated the action of acetic anhydride on a number of substituted anilines, mostly at fairly high temperatures, and concluded that acid substituents (Cl, Br, NO_2) in ortho-positions tend to retard the formation of a monoacetyl derivative, but that when the one acetyl group has been introduced the same ortho-substituents facilitate the formation of a diacetyl compound. Thus an arylamine, like *s*-tribromoaniline, which contains two bromine atoms in ortho-positions with respect to the amino-group, is practically not acted on by acetic anhydride in the cold, but when boiled with an excess of the anhydride for an hour, gives a good yield of the diacetyl derivative.

No experiments have been described with arylamines containing positive substituents. As the work undertaken with the naphthylamines indicated that the α -compound is more readily diacetylated than the isomeric β -compound (pp. 539, 540), it was decided to compare the behaviour of arylamines containing a methyl group in an ortho-position with that of arylamines free from an ortho-substituent. The bases selected were aniline, *o*- and *p*-toluidine, and ψ -cumidine, and the action of acetic anhydride on them and on their monoacetyl derivatives has been studied.

The arylamine (1 mol.) was boiled for an hour with acetic anhydride (4 mols.) in a flask fitted with an air condenser and calcium chloride tube. The conditions were, as far as possible, kept the same, and at the end of the given time the excess of acetic anhydride was distilled off under reduced pressure, and the mono- and di-acetyl derivatives separately isolated by fractional crystallisation or by distillation under reduced pressure. The results obtained indicate that a base with a methyl group in an ortho-position, as in *o*-toluidine and ψ -cumidine, gives a better yield of diacetyl derivative than one in which an ortho-substituent is not present.

When the monoacetyl derivatives were employed, 1 mol. was boiled for an hour with 2 mols. of acetic anhydride, and the product then treated as in the previous cases. The results obtained were very similar to those given by the bases themselves.

These results, taken in conjunction with those of Ulffers and von Janson, indicate that a substituent, whether of positive or negative character in the ortho-position to an amino-group of a primary arylamine, facilitates the formation of a diacetyl derivative. The results obtained so far do not enable conclusions to be drawn as to the

differences in the accelerating actions of different substituents, but I hope shortly to be able to undertake experiments with the object of settling this point.

The experiments described in this paper establish beyond doubt that the ordinary arylamines are much more readily diacetylated than is generally believed; for example, when aniline (1 mol.) and acetic anhydride (4 mols.) are boiled for an hour, 53 per cent. of the amine is converted into the diacetyl derivative, and other amines give even better yields.

The accelerating effect of ortho-substituents on diacetylation appears to be all the more remarkable when compared with previous work on di-ortho-substituted acids (*Ber.*, 1894, 27, 510, 1580, 3146; *Trans.*, 1895, 67, 587, 601; 1897, 71, 229), in which it has been shown that various reactions, most of which can be regarded as of an additive nature, are retarded by the presence of ortho-substituents. Emil Fischer too has shown (*Ber.*, 1900, 33, 345, 1967) that the presence of ortho-substituents in a tertiary aromatic amine of the type

 X
 Y
 NMe_2 completely inhibits the formation of quaternary ammonium compounds.

Ulfers and von Janson's observations that ortho-substituents retard the formation of monoacetyl derivatives renders the subject even more complex, as these same groups facilitate the introduction of a second acetyl group.

One of the simplest explanations of the process of acetylation by the aid of acetic anhydride, refers the production of the acetyl derivative to the formation of an additive compound of the arylamine and anhydride, which subsequently decomposes into the monoacetyl derivative and acetic acid:

The formation of a diacetyl compound may also be assumed to proceed in a similar manner,

If this actually represents the course of the reaction, then by analogy with other additive reactions the ortho-substituents would be expected to exert an inhibiting influence, whereas although they do seem to retard it to a certain extent in the first stage, they accelerate it in the second.

Are we to conclude that the processes of mono- and of di-acetylation are essentially different, or can a simple explanation be offered?

An explanation which presented itself to me, but for which at present absolutely no experimental proof can be produced, is as follows.

The additive products of the arylamines with acetic anhydride, the monoacetylarylamines acetates, will almost certainly be of varying degrees of stability, and as the diacetyl derivatives can only be formed after the decomposition of the additive compound, it would follow that the monoacetyl derivatives whose acetates are the least stable are most readily diacetylated.

It is a well-known fact that substituents in a succinic acid facilitate the removal of water and the formation of succinic anhydrides; in a similar manner, the ortho-substituent may facilitate the removal of acetic acid from the additive compound, and in this way accelerate the formation of a diacetyl derivative.

All attempts to isolate the additive compounds have proved fruitless.

When acetanilide is crystallised from glacial acetic acid, or from a mixture of acetic acid and chloroform, the unaltered anilide is obtained. Further, when *p*-toluidine (1 mol.) is mixed with acetic anhydride (1 mol.) in a vessel surrounded by ice, the product does not set to a solid mass of aceto-*p*-toluidide acetate, but has a pasty appearance, and a strong odour of acetic acid, and when kept over sulphuric acid for some time leaves the monoacetyl derivative.

EXPERIMENTAL.

Acetylation of Aniline.

Aniline (10 grams) was boiled for 1 hour with acetic anhydride (44 grams) and the excess of anhydride and acetic acid distilled off under reduced pressure, the distillation being continued until the temperature rapidly rose to about 120°. The residue in the flask was mixed with a little benzene, and, on cooling, crystals of acetanilide were deposited; a little light petroleum (b. p. 80—90°) was then added, when a further quantity of acetanilide was obtained. The mother liquor was evaporated, and the residue crystallised from a considerable amount of light petroleum (b. p. 40—50°), when the diacetyl derivative was obtained in the form of glistening plates melting at 37°. The small amount of residue, insoluble in light petroleum, gave, on crystallisation from benzene, a further quantity of acetanilide.

The amounts obtained were:

	Grams.	M. p.	Per cent.
Monoacetyl.....	5.6	114°	38.5
Diacetyl	10.0	37	53

Acetanilide (10 grams) and acetic anhydride (16 grams) were then

boiled for an hour, and the product treated in exactly the same manner as described above; the amounts obtained were:

	Grams.	M. p.	Per cent.
Monoacetyl.....	3.0	114°	30
Diacetyl	8.7	37	66

The melting point of diacetylaniline, as given by Kay (*loc. cit.*), is 37—37.5°.

Acetylation of o-Toluidine.

o-Toluidine (10 grams) and acetic anhydride (38 grams) were boiled together for an hour, the excess of acetic anhydride was distilled off under reduced pressure, a little benzene and light petroleum were added to the residue in the flask, when a small amount of monoacetyl derivative melting at 110° was obtained. The benzene and light petroleum were distilled off, and the residual oil distilled under diminished pressure; nearly the whole passed over at 152—153° under 20 mm. pressure, and only a slight residue remained in the flask. From the latter, a minute quantity of monoacetyl derivative was obtained. The diacetyl-*o*-toluidine, when kept for some time, deposited extremely well-developed pyramids melting at about 18°; Kay gives the boiling point as 150—151° under 16 mm. pressure, and Clayton (*Ber.*, 1895, 28, 1665) the melting point as 18°.

The amounts obtained were:

	Grams.	M. p.	Per cent.
Monoacetyl.....	1	110°	7
Diacetyl	14.5	18	81

Ten grams of aceto-*o*-toluidide were boiled for an hour with 14 grams of acetic anhydride, and the product distilled under reduced pressure; 12 grams of oil distilling at 152—153° under 20 mm. pressure were obtained. The residue in the flask gave 0.25 gram of unaltered monoacetyl derivative.

Acetylation of p-Toluidine.

This was carried out in precisely the same manner as described for the ortho-compound. On the addition of benzene, after removal of the acetic anhydride, colourless crystals of the monoacetyl derivative, melting at 148—149°, were obtained. The mother liquor was distilled under reduced pressure, and 9.6 grams of an oil obtained which passed over at 167—168° under 22—23 mm. pressure. When cold, this set into a mass of colourless crystals melting at about 40°, and after recrystallisation from light petroleum at 48°. Kay gives the boiling point of diacetyl-*p*-toluidine as 160—161° under 15 mm. pressure, and Clayton the melting point as 48°. The quantities obtained were:

	Grams.	M. p.	Per cent.
Monoacetyl.....	4.5	149°	32.3
Diacetyl	10.7	47	60.0

An experiment was then made by heating aceto-*p*-toluidide (10 grams) with acetic anhydride (14 grams) for an hour. The products were separated as in the previous case, and the results obtained were :

	Grams.	M. p.	Per cent.
Monoacetyl.....	2.4	150°	24
Diacetyl	9.2	48	72

Acetylation of ψ -Cumidine, $C_6H_2Me_3 \cdot NH_2$, $[NH_2 : Me_3 = 1 : 2 : 4 : 5]$.

Ten grams of the base and 30 grams of acetic anhydride were boiled for an hour, and the excess of anhydride distilled off under reduced pressure. The oily residue solidified on cooling, and was then extracted with warm light petroleum (b. p. 50—60°). The monoacetyl derivative was left behind in the form of a fine powder which, after recrystallisation from dilute alcohol, formed colourless needles melting at 161°.

The diacetyl compound, $C_6H_2Me_3 \cdot NAc_2$, crystallised from the light petroleum in extremely well-defined, hard, transparent prisms, but usually mixed with a small amount of the monoacetyl compound, from which it was freed by recrystallisation. It melts at 59.5°, and is readily soluble in all the ordinary organic solvents, but insoluble in water. On analysis :

0.3908 gave 21.1 c.c. moist nitrogen at 15° and 768 mm. $N = 6.4$.

$C_{13}H_{17}O_2N$ requires $N = 6.4$ per cent.

0.2 gram was boiled with 50 c.c. of standard barium hydroxide solution (protected from atmospheric carbon dioxide) for a few minutes until all the oil had disappeared, and then titrated with standard sulphuric acid (1 c.c. = 0.0088 gram), using phenolphthalein as indicator ; 12.2 c.c. of the acid were required in one experiment, and 12.3 c.c. in a second. A blank experiment in which 50 c.c. of the barium hydroxide solution were boiled without the addition of the diacetyl compound required 17.3 c.c. of acid. Hence the amount of acetyl = 19.5, that calculated being 19.6 per cent., provided only one acetyl group is removed. The precipitate, consisting of barium sulphate and the product of hydrolysis, was extracted with dilute alcohol, and colourless needles of the monoacetyl derivative melting at 162° were obtained. Boiling with baryta water for a few minutes thus removes one of the acetyl groups, but leaves the other intact.

Shaking the diacetyl derivative with dilute sodium hydroxide solution has a similar action, but is somewhat more difficult to regulate,

owing to the fact that the compound clots together, and thus is not acted on by the alkali. Boiling with aqueous or alcoholic soda for several hours does not completely remove the two acetyl groups (compare Kay, *loc. cit.*).

The weights of mono- and di-acetyl derivatives obtained from 10 grams of the base were :

	Grams.	M. p.	Per cent.
Monoacetyl.....	1.3	161—162°	10
Diacetyl	13.7	59.5	85

An experiment was then made by heating the monoacetyl compound (10 grams) with acetic anhydride (12 grams) for an hour, and the product separated as before :

	Grams.	M. p.	Per cent.
Monoacetyl	0.8	161°	8
Diacetyl	11.0	59.5	89

Acetylation of α -Naphthylamine.

Ten grams of the base were boiled for an hour with 28.6 grams of acetic anhydride ; when cold, a considerable amount of well-defined, prismatic crystals separated. The excess of acetic anhydride was removed by distillation under reduced pressure, and the residue then fractionally crystallised from ethyl alcohol. The diacetyl derivative crystallises first in the form of well-developed, hard prisms ; these are followed by a mixture of mono- and di-acetyl derivatives, which may be separated mechanically as the monoacetyl compound crystallises in feathery needles and the diacetyl in fairly large prisms ; a small amount of the mixed acetyl derivatives is finally obtained, which could not be separated into its constituents. The amounts obtained were :

	Grams.	M. p.	Per cent.
Monoacetyl	1.9	159°	14.7
Diacetyl	11.9	130	75.0

Diacetyl- α -naphthylamine crystallises readily from most organic solvents. It is deposited from its alcoholic or benzene solutions in well-developed, slightly opaque, colourless crystals, having a striated structure somewhat resembling that of potassium iodide crystals. It melts at 130°, and loses one of its acetyl groups when boiled with aqueous alkalis. 0.3 gram was boiled for half an hour with 50 c.c. of standard barium hydroxide solution, and then required 10 c.c. of sulphuric acid (1 c.c. = 0.0088 gram) for neutralisation, using phenolphthalein as indicator. Fifty c.c. of the baryta water, when boiled alone in a similar manner, required 17.3 c.c. of sulphuric acid for neutralisation. Hence the amount of acetyl = 18.8, that calculated being 19.0 per cent. provided only one acetyl group is removed. Although there was a

slight odour of α -naphthylamine after boiling with the alkali, the product obtained was found to be acet- α -naphthalide, as when crystallised from dilute alcohol it melted at 159° .

On analysis of the diacetyl derivative, the following numbers were obtained :

0.4 gave 21.8 c.c. moist nitrogen at 12° and 755 mm. N = 6.4.

0.4079 „ 22.5 c.c. „ „ „ 14° „ 754 „ N = 6.4.

$C_{14}H_{13}O_2N$ requires N = 6.2 per cent.

Acetylation of β -Naphthylamine.

The acetylation of β -naphthylamine was performed in exactly the same manner as with the α -compound, and the excess of acetic anhydride removed by distillation under reduced pressure. The residue had a somewhat syrupy consistency, and did not crystallise at all readily; after trying several methods for the separation of the mono- and di-acetyl derivatives, the following was found to give the best results.

The syrupy residue was dissolved in slightly more than its own volume of benzene and the acet- β -naphthalide which crystallised out was collected on a filter; light petroleum was added, when a further quantity of the monoacetyl derivative was obtained. The clear filtrate, when left to evaporate spontaneously, gave a crust of the diacetyl compound on the sides of the beaker; as this did not crystallise well, the whole of the benzene and light petroleum was removed by evaporation and the residue crystallised from light petroleum (b. p. $50-60^{\circ}$), when the diacetyl derivative was obtained in the form of clusters of snow-white plates melting at 66.5° . When crystallised from benzene, the small amount of residue insoluble in light petroleum gave about 0.5 gram of the monoacetyl derivative. The numbers obtained were :

	Grams.	M. p.	Per cent.
Monoacetyl.....	5.5	133°	42.5
Diacetyl	7.7	66.5	48.5

Diacetyl- β -naphthylamine, $C_{10}H_7 \cdot NAc_2$, crystallises from light petroleum or from dilute alcohol in colourless plates melting at 66.5° and readily soluble in most organic solvents.

0.771 gave 40.9 c.c. nitrogen at 10° and 756 mm. N = 6.3.

0.4563 „ 24.9 c.c. „ „ „ 16° „ 740 „ N = 6.2.

$C_{14}H_{13}O_2N$ requires N = 6.2 per cent.

It appears to be less readily hydrolysed than the α -compound, as when boiled with excess of baryta water for an hour it was not completely decomposed into the monoacetyl derivative. 0.5 gram was

boiled in a reflux apparatus fitted with a soda-lime tube for an hour with 10 c.c. of methyl alcoholic potash, the solution then required 38.0 c.c. of sulphuric acid (1 c.c. = 0.0088 gram) for neutralisation, and as 10 c.c. of the original alcoholic potash required 50.3 c.c. of sulphuric acid, the amount of acetyl = 19.0, that calculated being 19.0 per cent. provided only one acetyl group is removed. The melting point of the product was 132.5°, proving it to be acet- β -naphthalide.

Acetylation of 2:6-Dibromoaniline.

A good yield of diacetyl-2:6-dibromoaniline, $C_6H_3Br_2 \cdot NAc_2$, is obtained when 2:6-dibromoaniline (1 mol.) is boiled for an hour with acetic anhydride (4 mols.). The product is poured into water and after standing for some time, filtered, dried, and crystallised from light petroleum (b. p. 80—90°). It forms well-developed, hard, transparent prisms melting at 100—101° and readily soluble in the usual organic solvents.

0.1789 gave 0.2038 AgBr. Br = 48.47.

0.1735 „ 0.1974 AgBr. Br = 48.41.

$C_{10}H_9O_2NBr_2$ requires Br = 47.8 per cent.

I hope shortly to be able to start experiments in order to determine the relative influence of different ortho-substituents (Me, Cl, Br, I, NO_2 , &c.) both on the formation and hydrolysis of mono- and di-acetylarylamines.

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