XLV.—*Acylation as Influenced by Steric Hindrance : the Action of Acid Anhydrides on 3:5-Dinitro-*p*-aminophenol.*

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IN compounds of the type of *isopicramic acid* (I) the "protection" of the hydroxyl is so effective that methylation by methyl sulphate and alkali completely fails to attack this group, the amino-group alone being attacked, with the final formation of those quinone-ammonium derivatives which have been described in a series of papers formerly communicated to, and published by, the Society :

The isomeric 3:5-dinitro-*p*-aminophenol (II above: Reverdin, *Arch. Sci. phys. nat.*, 1904, [iv], 18, 342; 1905, 19, 353) shows an equally "protected" amino-group, so that methylating agents in this case fail to attack this group. The corresponding dinitro-anisidine can be readily prepared by the action of methyl iodide on the silver salt of the monoacetyl derivative and hydrolysis of the product (Meldola and Stephens, T., 1905, 87, 1206), but the methylation of the amino-group cannot be effected by methyl sulphate alone, whilst alkaline methylating agents are inapplicable on account of the tendency of the free alkali to cause complete decomposition with removal of a nitro-group. In these circumstances it became of interest to study the influence of configuration on the introduction of acid radicles, it being well known that under ordinary conditions unprotected amino-groups are much more readily acylated than similarly unprotected hydroxyl groups. Thus *isopicramic acid* quite readily gives a monoacetyl derivative (acetyl-amino-compound) when boiled for a few minutes in acetic acid solution with acetic anhydride. The hydroxyl in this compound is only attacked when the monoacetyl derivative is dissolved in undiluted acetic anhydride mixed with a little concentrated sulphuric acid. From this point of view, the action of acetic anhydride on 3:5-dinitro-*p*-aminophenol has been studied under

* This formula is assigned to the free compound; in solution it may have a quinonoid structure (Meldola and Hewitt, T., 1913, 103, 880).

various conditions, and with results which appear of importance from several unexpected points of view.

In the first experiments the inertness of the compound towards acetic anhydride was revealed by the fact that acetylation in acetic anhydride at 100° only takes place after heating for several hours. Under these conditions the product proved to be mainly the known diacetyl derivative. The same diacetyl derivative is formed immediately on dissolving the dinitro-compound in acetic anhydride with the addition of sulphuric acid. From this diacetyl derivative the known monoacetyl derivative (m. p. 182—183°) can be most readily prepared by dissolving the diacetyl compound as rapidly as possible in cold dilute sodium hydroxide and precipitating by acid. The phenolic character of the product indicates that the *O*-acetyl is removed by the alkali. These first experiments resulted, therefore, simply in the production of the diacetyl derivative, and from the latter the *N*-monoacetyl derivative by quite normal methods.

Acetylation in Acetic Acid Solution.

In order to modify the action of the acetic anhydride, the latter was diluted with glacial acetic acid, and the experiments continued with this mixture. Under these conditions it was found that a non-phenolic substance was formed, the further investigation of which showed that the compound was isomeric with the known monoacetyl derivative. After many experiments the following method was found the most effective for the preparation of the new compound:

The dinitroaminophenol is dissolved in a small quantity of hot glacial acetic acid, and two to three times the theoretical quantity of acetic anhydride necessary for the introduction of one acetyl group added to the solution. The latter is then boiled for half-an-hour, and when cold poured into water so as to precipitate the product. If the heating is prolonged beyond the time specified, the yield is diminished; three or four hours' boiling appears to destroy the compound completely. The crude product is collected, washed, and purified by first washing with a little dilute alkali, then with water, and finally crystallising from alcohol or acetic acid. The pure compound crystallises in flat needles or scales of a golden-yellow colour; the melting point is 185—186°. A mixture of the substance with the isomeric monoacetyl derivative (m. p. 182—183°) melted at 151—156°:

0.1026 gave 0.1500 CO₂ and 0.0282 H₂O. C=39.87; H=3.05.

0.1090 „ 0.1588 CO₂ „ 0.0284 H₂O. C=39.73; H=2.89.

0.0898 „ 13.7 c.c. N₂ (moist) at 21° and 762.8 mm. N=17.43.

C₈H₇O₆N₃ requires C=39.82; H=2.93; N=17.43 per cent.

These results leave no doubt as to the isomerism between the two acetyl derivatives.

3:5-Dinitro-O-acetyl-p-aminophenol.

In discussing formulæ for the new compound, its properties as compared with those of its isomeride had to be considered. The *N*-acetyl derivative when pure crystallises in nearly white needles, extremely soluble in alcohol, and distinctly phenolic in character. The new compound is fairly stable towards alkali, and not very readily soluble in alcohol. It is very stable under the influence of heat, and can be partly sublimed without decomposition when heated in a dry tube. The most striking visible difference between the isomerides is the intense yellow colour of the new compound. The chemical properties of the latter are at first sight quite in harmony with the view that it is the *O*-acetyl derivative:

On further acetylation with acetic anhydride in presence of a little sulphuric acid it gives the known diacetyl derivative identical with that obtained by the direct acetylation of the dinitro-compound. When hydrolysed by sulphuric acid it gives 3:5-dinitro-*p*-aminophenol; it imparts a transitory violet colour to an alkali hydroxide solution, this colour being due to the dinitro-compound liberated by hydrolysis. The free dinitro-compound has the same property, the transient violet colour being due to the alkaline salt which is at first formed, but decomposes in presence of excess of alkali. Boiling with sodium carbonate solution also effects hydrolysis, and the violet solution of the sodium salt on acidification gives 3:5-dinitro-*p*-aminophenol. Attempts to methylate the amino-group by methyl sulphate under various conditions gave negative results. The compound dissolves much more freely in methyl sulphate than the isomeric *N*-acetyl derivative, but the solution after being kept at 100° for an hour was found to contain only the original dinitroaminophenol, the methyl sulphate acting simply as a hydrolysing agent.

These properties all point to the conclusion that the new compound is the expected *O*-acetyl derivative; nevertheless, its colour and the extreme readiness with which it is formed seem to indicate that the simple formula given above does not adequately represent the whole of the ascertained facts. The acetylation of a true phenolic hydroxyl group by simply boiling for a short time with

acetic anhydride diluted with acetic acid is, as already stated, most unusual. Moreover, such phenolic acetates, even when containing several nitro-groups, are never very highly coloured. The colour of the present compound suggested, therefore, that the amino-group was implicated, and the formulæ given below have been considered :

Of these formulæ, I is disposed of by the fact that no evidence of interconvertibility of the isomerides has been observed; all attempts to convert the *N*-acetyl derivative into the isomeride and vice versa have led to negative results. Between II and III it is not so easy to decide, but the absence of acidic character and general analogy to similarly constituted nitroamino-compounds leads us to adopt the "inner salt" formula (III) as the most probable.

It follows from these conclusions that the isomerides are of different types of benzenoid structure, the *N*-acetyl derivative being incapable of forming an "inner nitrolic salt" on account of the attachment of the acid radicle to the 4*N*-atom, whilst the *O*-acetyl derivative containing a nitro-group ortho to the 4*NH*₂-group is capable of "inner salt" formation, with consequent orthoquinonoid structure. Specimens of the isomerides were kindly examined for us spectroscopically by Dr. J. T. Hewitt, by whom the accompanying curves representing the absorption spectra have been prepared. It will be seen that the absorption spectrum of the *O*-acetyl compound is quite different in type from that of the *N*-acetyl derivative.

We may add that in deciding in favour of the above formula (III) we have had also under consideration the results of certain experiments devised with the express object of getting evidence as to paraquinonoid structure (I) and nitrolic acid structure (II); thus the non-phenolic acetyl derivative is not profoundly affected by such reagents as hydroxylamine, hydrazine, or phenylhydrazine, all of which simply act as hydrolysing agents. An attempt to form a nitrolic salt by adding sodium ethoxide to the toluene solution of the compound also led to a negative result. The whole of the compound is precipitated by this means as a brown, amorphous substance, which is the same product as that which results from the decomposition of the original dinitro-compound by the same method. Sodium ethoxide does not, therefore, form a nitrolic salt,

but simply removes the *O*-acetyl, and then decomposes the dinitro-compound with the formation of the usual indefinite products.

The Colour of Nitroaminophenols and their Derivatives in Relation to their Constitution.

This conclusion concerning the constitution of the *O*-acetyl derivative warrants the extension of the same type of structure to the

Scale of oscillation frequencies.

original (unacetylated) compound, and, generally, to all the nitroaminophenols and their derivatives which have been under investigation in our laboratory for many years. The condition essential for the production of highly-coloured compounds appears to be the ortho-position of a nitro-group with respect to an amino-group or a

substituted amino-group. The presence of additional nitro-groups in the nucleus has generally the effect of increasing the intensity of the colour. From this point of view 3:5-dinitro-*p*-aminophenol would have the formula (I) *:

The above compound is of a deep red colour, all analogously constituted compounds being more or less red and far more highly coloured than the mere presence of nitro- and amino-groups in the nucleus would account for unless some more profound change of structure is allowed; thus, *isopicramic acid*, in which there is no nitro-group ortho to an amino-group, is very feebly coloured (in the free state) as compared with the above isomeride. On the other hand, 2:3-dinitro-*p*-aminophenol (II above) is red (Meldola and Hay, T., 1907, **91**, 1482), and the corresponding 2:3-dinitro-*p*-anisidine deep orange (Meldola and Eyre, T., 1902, **81**, 990). 2:6-Dinitroanisidine (III) is ochreous (Meldola and Stephens, T., 1905, **87**, 1204) and 3:5-dinitroanisidine (IV) deep red (*ibid.*, p. 1206). 2:3:6-Trinitro-*p*-aminophenol (V) is also deep red (Meldola and Hay, T., 1909, **95**, 1380), as is the corresponding trinitroanisidine (Meldola and Kuntzen, T., 1910, **97**, 456). The isomeric 2:3:5-trinitro-*p*-anisidine (VI above) is also red (Reverdin and de Luc, *Arch. sci. phys. nat.*, 1909, [iv], **27**, 383). A detailed comparative study of the absorption spectra will be necessary to complete the evidence from the optical side. So far as observations with these compounds have hitherto been carried out, it is instructive to compare the curves representing the absorption spectra of 2:3:5-trinitro-*p*-anisidine and of its acetyl derivative (in which no inner salt formation is possible) given in a former paper (Meldola and Hewitt, T., 1913, **103**, 884) with those given in the present communication.

* This structural formula may explain the inertness of the amino-group towards acylating agents, although "steric hindrance" must also be allowed for, since the 5-nitro-group would act as a "protecting" group.

Preparation of the O-Propionyl Derivative.

The extreme readiness with which the hydroxyl group of the dinitro-compound can be acetylated suggested the application of the foregoing method for the introduction of other acid radicles. It will no doubt be found possible to acylate the hydroxyl group of 3:5-dinitro-*p*-aminophenol by means of the higher homologues of acetic anhydride generally. A preliminary experiment with propionic anhydride diluted with propionic acid carried out in precisely the same way as with acetic anhydride showed that the *O*-propionyl derivative could be prepared with equal readiness. This compound has all the properties of its lower homologue; it crystallises from alcohol in flat, golden-yellow needles, melting at 172—173°:

0.1022 gave 0.1588 CO₂ and 0.0354 H₂O. C=42.38; H=3.85.

0.1274 „ 18.5 c.c. N₂ (moist) at 23° and 760.5 mm. N=16.37.

C₉H₉O₆N₃ requires C=42.34; H=3.55; N=16.47 per cent.

The compound is therefore 3:5-dinitro-*O*-propionyl-*p*-aminophenol,

Attempt to Prepare the O-Benzoyl Derivative.

An attempt to introduce benzoyl by the same method led to an interesting result. The dinitro-compound was boiled as before with benzoic anhydride dissolved in glacial acetic acid. The product proved, however, to be the *O*-acetyl derivative previously described. In this case, therefore, the benzoic anhydride simply promotes the acetylation, or else the benzoyl derivative is first formed and then converted into the acetyl derivative by interchange of radicles.*

Whether the protection of the amino-group by ortho-substituents is exerted equally by radicles other than the nitro-group yet remains to be investigated. The corresponding 3:5-dihaloid-*p*-aminophenols, so far as we have been able to ascertain, do not appear to be known, and their preparation will be attempted in order to throw further light on this question.

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* The dinitro-compound is not acetylated by boiling for many hours with acetic acid alone.