

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF FORDHAM UNIVERSITY]¹

FURTHER INVESTIGATIONS ON THE NITRATION OF AROMATIC COMPOUNDS WITH METALLIC NITRATES

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I. Theoretical Part

Nitrates have repeatedly been used to perform nitrations in the aromatic series; nevertheless, their role formerly consisted of the production of nitric acid when an especially concentrated nitric acid had to be used, as in the case of benzoic acid when nitrated to *m*-nitrobenzoic acid. Inasmuch as in such cases the nitrate was always mixed with sulfuric acid, we hardly speak of a nitration by the nitrate, since it was the nitric acid that brought about the reaction.

Based on the formation of diacetyl ortho-nitric acid when concd. nitric acid is distilled with acetic anhydride, and of acetyl nitrate when nitric acid and acetic anhydride are mixed at low temperature, Menke² thought that the nitrates of copper, iron, etc., might lead to the same aliphatic compounds as the "nitrate of H," nitric acid. Inasmuch as diacetyl ortho-nitric acid and acetyl nitrate are both efficient nitrating agents, and can be used without being isolated, Menke thought of using mixtures of metallic nitrates and acetic anhydride or glacial acetic acid to perform nitrations. To this effect he published data of nitrations performed by the action of mixtures of cupric nitrate and ferrous nitrate with acetic anhydride or glacial acetic acid on aceto-acetic ester, aniline and phenol. In the case of aniline he obtained *o*-nitro-aniline; with phenol he obtained *o*-nitrophenol when glacial acetic acid is used, and picric acid when acetic anhydride is employed. He has also used in one experiment a mixture with acetyl chloride, in which case chloro-nitration was the result. He further asserts, without giving any data, that very similar results were obtained with the nitrates of nickel, cobalt, aluminum, cerium and uranium, and also makes the statement that the nitrates of the alkali metals have no action. In addition to this, and again without giving any experimental data, he says that the following substances also have been tested as to their nitratability with nitrates: benzene, toluene, dimethylaniline, diphenylamine and naphthalene, and that they all could be nitrated with the exception of naphthalene.

It must be emphasized that the *o*-nitro-acetanilide and *o*-nitrophenol thus obtained, according to Menke, were practically pure. The apparently excellent results obtained by Menke in his nitrations of aniline and

¹ The above investigation was authorized and approved by Richard Martin, Head of the Department of Chemistry.

² Menke, *Rec. trav. chim.*, **44**, 141, 270 (1925); (b) Brit. pat. 235,698, (1924).

phenol by means of inorganic nitrates, whereby he claims to have received one of the isomers only, as well as the remarkable facility of the operation, induced the author of this paper to make further investigations in this field, with a view of broadening the subject as to the application of this method to various cases under varying circumstances. To this effect we endeavored to find an answer to a number of most essential questions which Menke does not attempt to solve. (1) Is this method of nitration a general or a selective one, that is, does it apply to all classes of aromatic compounds or to only a selected group of them? (2) Are there nitrates which behave in a different manner from those employed by Menke, so as to give us a different isomer, that is, is there a relationship between the nature of a particular nitrate and the structure of the resulting nitro compound? (3) Can we change the experimental conditions with a given nitrate so as to obtain at will one isomer or another?

We should mention here that in 1926 Spiegel and Haymann³ published results obtained with bismuth nitrate, either alone or in the presence of acetic anhydride. They endeavored to nitrate aniline, phenol and anisole and their results were different from Menke's in that they obtained mixtures of *o*- and *p*-nitro derivatives instead of practically pure *ortho* compounds. Their further attempts to nitrate benzene, toluene, *p*- and *o*-xylene, β -naphthol, nitrobenzene and *p*-toluidine were all negative.

These findings, somewhat different from Menke's, show how justified we were in making further investigations.

To answer Question 1 we tried the action of cupric nitrate and ferric nitrate on benzaldehyde, benzoic acid, nitrobenzene and *p*-toluidine; the experiments with benzaldehyde, benzoic acid and nitrobenzene were carried out at various temperatures but the results were negative throughout. Entirely different were the results obtained with *p*-toluidine, which could be nitrated with the greatest facility. If we now compare these results with those obtained by Menke, and by Spiegel and Haymann, we notice that the nitration of aromatic compounds with inorganic nitrates seems to be possible only with hydrocarbons or compounds which contain groups of the first class, while substances with second-class groups only apparently remain unaffected.

The answer to our first question seems to be, therefore, that this method is a selective one, compounds having only second-class groups being excluded.

The object of our second question was to compare the action of a number of nitrates in order to find out whether or not there is a relationship between the nature of a given nitrate and the structure of the resulting nitro compound, and also to study the particular conditions of reaction of the various nitrates.

³ Spiegel and Haymann, *Ber.*, 59, 202 (1926).

To this effect we studied the action of the nitrates of iron, manganese, cobalt, nickel, copper, mercury, silver, sodium and lithium on *p*-toluidine. The experiments were conducted in much the same way as those mentioned above. *p*-Toluidine at first, of course, reacted with acetic anhydride or glacial acetic acid to form acetotoluide or acetyl toluidine. Then nitration set in and we obtained 3-nitro-*p*-acetotoluide. The above-mentioned nitrates all yielded the same product with the exception of silver nitrate and sodium nitrate, which gave no results at all. It is interesting to note that while sodium nitrate and silver nitrate did not produce nitration, nitration was obtained with lithium nitrate, and thus Menke's statement to the effect that alkali metallic nitrates do not tend to nitrate must be revised, at least in behalf of lithium nitrate. In comparing the velocity of the reactions we found that the greatest speed was shown by cupric nitrate; the reaction could be performed in ten minutes at a temperature of 30°. Next in velocity came the nitrates of the iron-class metals; the time to nitrate the same amount of *p*-toluidine was from 15 to 20 minutes and the temperature ranged from 65 to 85°. The action of all of the nitrates of the iron-class metals is very much the same, and the same data hold true in the case of mercurous nitrate. An entirely different aspect is presented by the action of lithium nitrate. Owing to the great stability of this compound, we submitted the mixture of *p*-toluidine, the nitrate and the solvent to boiling under reflux. The mixture was tested frequently in order to detect the setting in of nitration; the reaction was completed at the end of two hours. The yield, however, was lower than that obtained in the preceding experiments.

The results obtained with lithium nitrate on *p*-toluidine also prompted the author to study the action of this nitrate on aniline, especially in view of Menke's statement that the alkali metallic nitrates are practically inactive.

The experiments with aniline were carried out in exactly the same way as those with *p*-toluidine. In both cases the mixture was boiled for two hours under reflux. The outcome of this experiment is very interesting, inasmuch as we obtained pure *p*-nitro-acetanilide instead of the *ortho* isomer, as reported by Menke, in connection with heavy metallic nitrates. In comparing these results we see that there seems to be a relationship between the nature of the nitrate and the resulting nitro product. The expression "nature of the nitrate" is to be taken in a broad sense, for we believe that it is not so much the nature of a given nitrate which is the primary cause of these differences as the fact that one type of nitrate reacts at a relatively low temperature and produces acetyl nitrate as the actual nitrating agent, while lithium nitrate, acting at a higher temperature, might also form diacetyl *ortho*-nitric acid. Pictet and Genequand⁴

⁴ Pictet and Genequand, *Ber.*, 35, 2526 (1902); 36, 2225 (1903).

and Pictet and Khotinsky⁵ have prepared both of these aliphatic nitrates and performed nitrations with them. Then, also, the temperature at which the nitration with the heavy metallic and alkali metallic nitrates takes place certainly has something to do with the formation of *ortho* and *para* nitro compounds.

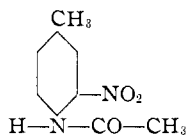
Question 3 asks if we can change the experimental conditions with a given nitrate so as to obtain a different isomer every time. We must answer this in the negative. In all cases nitration takes place between definite limits of temperature, according to the nitrate used, and for a given nitrate the final product is always the same.

II. Experimental Part

Nitration of *p*-Toluidine with Cupric Nitrate.—Ten g. of cupric nitrate, $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$, was pulverized in a mortar and introduced into a mixture of 20 g. of acetic anhydride and 10 g. of glacial acetic acid. The temperature slowly rose to 35° when, drop by drop, a solution of 5 g. of *p*-toluidine in 6 g. of acetic anhydride and 4 g. of glacial acetic acid was added. The temperature was kept at 35° throughout the experiment and no evolution of nitrogen dioxide took place. After ten minutes the mass was slowly introduced into 150 cc. of ice-cold water. Immediately a yellow precipitate settled out and after a short while was filtered off by suction. It was redissolved by heating in a minimum of a 40% solution of alcohol and allowed to recrystallize. Long, yellow needles settled out which were again filtered by suction and air-dried; m. p., 94° . When these crystals were dissolved without heating in 95% alcohol and the alcohol was allowed to evaporate slowly, a white precipitate appeared, and it was found that this substance when heated to 88° became yellow again and showed the former melting point of 94° .

Anal. (Dumas.) Calcd. for $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_3$: N, 14.43. Found: 14.71.

The substance, therefore, is 3-nitro-*p*-acetotoluide,



the methyl group being in Position 1. This compound exists in two allotropic forms, a yellow, and a white form which upon heating is transformed into the yellow form⁶ again.

Nitration of *p*-Toluidine with Ferric Nitrate.—Ten g. of ferric nitrate, $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$, was reduced to a fine powder in a mortar and introduced into a mixture of 60 g. of acetic anhydride and 40 g. of glacial acetic acid. To this was then slowly added a solution of 9 g. of *p*-toluidine in 10 g. of acetic anhydride and 5 g. of glacial acetic acid. Tests showed that the nitration did not take place below 60° , and therefore the temperature was kept between 60 and 80° throughout the procedure. The addition of the *p*-toluidine took 20 minutes, after which the mixture was allowed to stand for another five minutes and was finally introduced into 250 cc. of water. A yellow precipitate formed which was filtered off by suction and redissolved by heating in a small amount of 40% alcohol. Upon cooling, the same yellow needles crystallized out as before. They were filtered off by suction and air-dried, and showed the same melting point as

⁵ Pictet and Khotinsky, *Ber.*, 40, 1163 (1907).

⁶ Gattermann, *Ber.*, 23, 1733 (1890).

the substance obtained in the preceding experiment. Since this substance had otherwise all the characteristics of that obtained with cupric nitrate, we must conclude that it is also 3-nitro-*p*-acetotoluide.⁷

Nitration of *p*-Toluidine with Mercurous Nitrate.—A mixture of 12 g. of mercurous nitrate and 5 g. of *p*-toluidine was introduced into 60 cc. of glacial acetic acid and heated for 20 minutes on a water-bath at a temperature of 70°. The mass was then allowed to cool and was finally introduced into 200 cc. of ice-cold water. The same yellow precipitate appeared as that obtained in the preceding experiments. After having been filtered off by suction and redissolved in 50 cc. of a 30% solution of alcohol, to which a small amount of animal charcoal had been added, the precipitate was filtered hot and, upon cooling, the yellow needles recrystallized. After having dried them, the melting point was found to be 94°. Furthermore, since the substance showed the same allotropic characteristics as that described in connection with cupric and ferric nitrates, we conclude that again it is 3-nitro-*p*-acetotoluide.

Nitration of *p*-Toluidine with Lithium Nitrate.—A mixture of 10 g. of *p*-toluidine and 7 g. of lithium nitrate was introduced into a round-bottomed flask containing 70 cc. of acetic anhydride. Owing to the great stability of alkali nitrates, the mixture was kept boiling under reflux for two hours. The mass became dark brown, only a slight amount of nitrogen dioxide being given off. After two hours it was allowed to cool and was then slowly added to 200 cc. of ice-cold water. A tarry mass settled out but no crystals appeared, even upon letting the mixture stand for several hours. Animal charcoal was then added, the mass heated and kept boiling gently for ten minutes, after which it was filtered off hot. Upon being allowed to stand for several hours, a brown, crystalline precipitate formed. It was filtered by suction, redissolved by heating in a 30% solution of alcohol to which a small amount of animal charcoal was added, and again filtered hot. Immediately, a yellow precipitate settled out. It was filtered by suction and dried, m. p. 94°, and upon recrystallizing a small quantity from 95% alcohol we obtained it in the white form. It is, therefore, the same product as already described above in connection with the other experiments. Because of the repeated charcoaling, the yield was smaller than that resulting from the other nitrates.

Para Nitration of Aniline with Lithium Nitrate.—To a mixture of 7 g. of lithium nitrate and 40 cc. of acetic anhydride was added 10 g. of aniline. The mixture was kept boiling for two hours under reflux and, as in the preceding case, it became dark brown and also gave off a slight amount of nitrogen dioxide. An excess of aniline was driven out by steam distillation. The mixture was then allowed to cool and was introduced into 200 cc. of cold water. As in the case of *p*-toluidine, a tarry mass settled out gradually. No crystals appeared, even upon allowing the mixture to stand for 12 hours. Animal charcoal was then added and the mass kept boiling for ten minutes, after which it was filtered hot. Upon cooling and allowing it to stand for 12 hours more, a crystalline, brown precipitate appeared. It was filtered by suction, redissolved in a 30% solution of alcohol to which charcoal had been added, and again filtered hot. Immediately a cream-colored precipitate appeared; it was filtered by suction and dried; m. p., 207°.

Anal. (Dumas.) Calcd. for C₈H₈N₂O₃: N, 15.55. Found: 15.64.

This proves that it is *p*-nitro-acetanilide. Again, due to repeated charcoaling, the yield was not as abundant as in the other experiments.

Action of Cupric Nitrate on Benzoic Acid.—Ten g. of benzoic acid dissolved in 30 cc. of acetic anhydride was slowly introduced into a mixture of 12 g. of cupric nitrate and 30 cc. of acetic anhydride at a temperature of 20 to 30°. After 20 minutes, the mixture

⁷ Inasmuch as the nitrates of manganese, nickel and cobalt react almost in the same way as ferric nitrate, we omit the description of the experiments performed with them.

was introduced into 300 cc. of ice-cold water, and a yellowish precipitate settled out. It was filtered by suction, washed and allowed to dry, m. p. 117–118°, and the substance was redissolved in water containing a little alcohol and allowed to recrystallize. After having been dried, its melting point was found to be 120°. Inasmuch as a qualitative test revealed no nitrogen we concluded that it was unchanged benzoic acid. No nitration took place in this case.

The same experiment was then repeated at temperatures of 50°, 60° and 100° with the same result. We may, therefore, conclude that benzoic acid cannot be nitrated by this method.

Action of Cupric Nitrate on Benzaldehyde and Nitrobenzene.—The experiments outlined above in the case of benzoic acid were repeated with benzaldehyde and nitrobenzene and in every case we could distil off an almost quantitative amount of unchanged substance.

Summary

As a result of the foregoing experiments we may draw the following conclusions.

1. The nitrating action of metallic nitrates is a selective one.
2. This action seems to favor those aromatic compounds which contain groups of the first class, while compounds with second class groups apparently remain unaffected. It is interesting to note the difference between this and the action of nitric acid, with which compounds like nitrobenzene, benzoic acid, etc., can be nitrated into their respective *m*-nitro derivatives.
3. The "nature" of a particular nitrate apparently has an influence on the structure of the resulting nitro compound as exemplified by the formation of the *ortho* derivative with heavy metallic nitrates and to a certain extent also bismuth nitrate, and the *para* isomer with lithium nitrate in the nitration of acetanilide. This, however, seems not to be a general attitude, since all the nitrates gave with *p*-toluidine the same nitro derivative.

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SUBSTITUTED O-ALKYL HYDROXYLAMINES CHEMICALLY RELATED TO MEDICINALLY VALUABLE AMINES¹

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One of the most important chemical groups found in alkaloids and in a great many other drugs is the amino group. Except for their greater ease of oxidation, reduction and reaction with the carbonyl group, hydroxylamine and substituted hydroxylamines react chemically very much as do ammonia and the amines. However, in the past, probably be-

¹ This paper is based upon a thesis submitted by Randolph Thomas Major to the Faculty of the Graduate School of Princeton University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.