NEW POSSIBILITIES IN NITRATION
WITH A MIXTURE OF NITRIC ACID
AND ACETIC ANHYDRIDE

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S. S. Novikov, L. I. Khmel'nitskii, and T. S. Novikova

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences, USSR

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In recent years nitrofuran compounds have been increasingly recognized as chemotherapeutic preparations. An essential stage in their synthesis is that of nitration. The most widely used agent for the nitration of furan compounds is a mixture of nitric acid and acetic anhydride. For a long time the nature of a mixture of nitric acid and acetic anhydride was not entirely clear. It was considered that the primary nitrating agent is nitric acid itself, and the acetic anhydride was regarded merely as a diluent, useful for binding the water liberated in the course of the nitration [1]. Already in 1928, however, Menke in a study of the nitration of aromatic hydrocarbons noted not only the water-withdrawing power, but also the peculiar catalytic action of acetic anhydride. Particularly convincing experiments were carried out by Giller [3], who showed for the case of 2-furaldehyde that dilute nitric acid (at concentrations as low as 60%) gives practically the same results as 100% acid; moreover, the yield of nitration product was not raised by the addition of such a powerful water-withdrawing agent as phosphoric anhydride.

The chemical essentials of the processes occurring in the nitric acid-acetic anhydride system have been clarified considerably during the last 10-15 years. On the basis of the results of vapor pressure measurements [4, 5], studies of Raman spectra [6], infrared absorption spectra [7], and density, refractive index, and viscosity measurements [8] on mixtures of nitric acid and acetic anhydride, it has been proved that acetyl nitrate and nitrogen pentoxide are formed in these mixtures. The extent to which one or other of these substances is formed depends on the initial proportions of the components of the mixture. When the initial nitric acid content is less than 50 moles per cent, acetyl nitrate, and also acetic acid, is found in the mixture. The maximum formation of acetyl nitrate is attained at an initial nitric acid content of 50 moles per cent. With further increase in the proportion of nitric acid nitrogen pentoxide begins to appear, and the maximum formation of this is attained at an initial nitric acid content of 85-90 moles per cent. Up to this limit nitrogen pentoxide exists as covalent molecules. At an initial nitric acid content of above 85-90 moles per cent nitrogen pentoxide is dissociated into NO₂⁺ and NO₃⁻ ions, and only traces of acetyl nitrate are present; it has been shown [5] that in this concentration range the gas phase contains 85-95% of nitrogen pentoxide.

Various chemical equations have been proposed to describe the formation of acetyl nitrate and nitrogen pentoxide [8, 9]:

\[ \text{HNO}_3 + (\text{CH}_3\text{CO})_2\text{O} \rightleftharpoons \text{CH}_3\text{COONO}_2 + \text{CH}_3\text{COOH} \]  (1)
\[ \text{HNO}_3 + \text{CH}_3\text{COONO}_2 \rightleftharpoons \text{CH}_3\text{COOH} + \text{N}_2\text{O}_5 \]  (2)
\[ 2\text{HNO}_3 + (\text{CH}_3\text{CO})_2\text{O} \rightleftharpoons \text{N}_2\text{O}_5 + 2\text{CH}_3\text{COOH} \]  (3)
\[ 2\text{CH}_3\text{COONO}_2 \rightleftharpoons \text{N}_2\text{O}_5 + (\text{CH}_3\text{CO})_2\text{O} \]  (4)

It is not difficult to see that Equation (3) is the sum of Equations (1) and (2), from which, moreover, Equation (4) can be derived. As regards the identity of the nitrating principle in a mixture of nitric acid and acetic anhydride, Ingold and co-workers [9] consider that this part is played not by acetyl nitrate, but by nitrogen pentoxide, either directly in the form of a covalent molecule, or after dissociation as the nitronium cation. Bonnet [10] came to the same
conclusion on the basis of an investigation of the kinetics of the O-nitration of dinitrobenzyl alcohol; he found that the reaction is of second order with respect to nitric acid in accordance with Equation (3), whereas if nitration had been effected by acetyl nitrate the reaction would most probably have been of first order with respect to nitric acid in accordance with Equation (1) for the formation of acetyl nitrate. Paul [11] showed that in the nitration of benzene reaction is again of second order with respect to nitric acid.

The role of nitrating agent was attributed to nitrogen pentoxide in spite of the fact that the nitric acid content of the mixtures of nitric acid and acetic acid used did not exceed 50 moles per cent (only in a few experiments did it reach 68 moles per cent) so that conditions prevailed under which nitrogen pentoxide was not detected by the physical methods indicated above and a high content of acetyl nitrate was observed. Chemical experiment supports the view that nitrogen pentoxide is formed even under these conditions, but only in extremely small amount. The presence of small amounts of nitrogen pentoxide in these nitrating mixtures is supported also by the close resemblance of the ultraviolet spectra of binary mixtures of nitric acid and of nitrogen pentoxide with acetic anhydride with a content of the latter of above 90% [12]. Finally, it is remarkable that in their recent experiments on the nitration of methyl phenylalkyl ethers with pure acetyl nitrate prepared from acetyl chloride and silver nitrate in acetonitrile solution Norman and Radda [13] came to the conclusion that the nitrating principle was nitrogen pentoxide. On the other hand, Burton and Praill [14] suggested that as a result of the following polarization of acetyl nitrate (for which they provided experimental evidence) this substance may be a nitrating agent in its own right and not only in virtue of the formation of nitrogen pentoxide from it.

In a study of the action of a mixture of 70% nitric acid and acetic anhydride on alkenes and anisole Bordwell and Garbish [15] suggested that the nitrating mixture contains protonized acetyl nitrate molecules which have a more powerful nitrating action than molecules of acetyl nitrate itself. The nitric acid serves as protonizing means:

\[
\begin{align*}
\text{HNO}_3 + (\text{CH}_3\text{CO})_2\text{O} & \rightleftharpoons \text{CH}_3\text{COONO}_2 + \text{CH}_3\text{COOH} \\
2\text{HNO}_3 + (\text{CH}_3\text{CO})_2\text{O} & \rightleftharpoons (\text{CH}_3\text{COHONO}_2)^+ + \text{NO}_3^- + \text{CH}_3\text{COOH}
\end{align*}
\]

This scheme is in equally good accord with a nitration reaction of second order with respect to nitric acid as the scheme for the formation of nitrogen pentoxide in accordance with Equation (3). On addition of sulfuric acid the nitration is speeded up and becomes a first-order reaction [11]. This is also readily explained, for the protonization is then effected not by nitric, but by the stronger sulfuric acid, and in the over-all equation there is now one molecule of nitric acid [15].

\[
\begin{align*}
\text{HNO}_3 + (\text{CH}_3\text{CO})_2\text{O} & \rightleftharpoons \text{CH}_3\text{COONO}_2 + \text{CH}_3\text{COOH} \\
\text{H}_2\text{SO}_4 + \text{CH}_3\text{COONO}_2 & \rightleftharpoons (\text{CH}_3\text{COHONO}_2)^+ + \text{HSO}_4^- \\
\text{HNO}_3 + \text{H}_2\text{SO}_4 + (\text{CH}_3\text{CO})_2\text{O} & \rightleftharpoons (\text{CH}_3\text{COHONO}_2)^+ + \text{HSO}_4^- + \text{CH}_3\text{COOH}
\end{align*}
\]

Also, under the action of sulfuric acid the equilibrium is shifted toward the accumulation of protonized particles, as a result of which the rate of nitration is increased. In the nitration process protons are continuously regenerated, so that the action of the sulfuric acid does not stop, even when protons are taken in catalytic amount. Bordwell and Garbish admit the possibility of the dissociation of protonized acetyl nitrate with formation of a nitronium ion

\[
(\text{CH}_3\text{COHONO}_2)^+ \rightleftharpoons \text{CH}_3\text{COOH} + \text{NO}_2^+
\]

or nitrogen pentoxide

\[
(\text{CH}_3\text{COHONO}_2)^+ + \text{NO}_3^- \rightleftharpoons (\text{CH}_3\text{COOH}) + \text{N}_2\text{O}_5
\]