A study of the Mannich reaction in the isoxazole series

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ABSTRACT

3:5-Dimethyl-4-nitro isoxazole and 3-aryl-2-isoxazolin-5-ones were found to undergo the Mannich reaction readily at room temperature, affording in most cases unstable products. While the 5-methyl group was the active site with the former, the latter underwent reaction exclusively at the 4-position. The structures of the products were confirmed by spectral data. The Mannich bases from the isoxazolones were found to exist in three tautomeric modifications, contrary to earlier observations. Most of the products exhibited a high degree of antibacterial activity.

MANNICH bases derived from heterocycles were found to exhibit a variety of physiological properties such as antihypertensive, antispasmodic, antiphlogistic, antipyretic, analgesic and antibacterial activities. Of particular interest are the Mannich bases belonging to the isoxazole series which were found to possess pronounced physiological activity. However, the isoxazole Mannich bases were made mostly by indirect syntheses, the Mannich reaction being restricted to only a few 2-isoxazolin-5-ones. Further, with these isoxazolones, interesting and varying behaviour was reported with differently substituted isoxazolones. For instance, 3-methyl or 3-amino-4-phenyl-2-isoxazolin-5-one reacted in the 2H-tautomeric form while the 3-methyl and 3-phenyl analogues reacted in the 4H-form (for structures of these forms, see Chart I).

![Chart I](image-url)

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MANNICH BASES DERIVED FROM 3:5-DIMETHYL-4-NITRO ISOXAZOLE (I);

Hence, it has been considered worthwhile to carry out the Mannich reaction in the isoxazole series with a view to studying the reactivity of the isoxazole nucleus when active centres are present and to examine the physiological activity of the resulting Mannich bases. For this purpose, two isoxazole systems possessing centres of reactivity have been chosen, viz., 3:5-dimethyl-4-nitro isoxazole (I) and 3-aryl-2-isoxazolin-5-ones (III) (vide Chart II) and the results of the investigations are presented below.

\[ \text{O}_2\text{N}^\text{CH}_3 \text{HCHO} \xrightarrow{\text{R}_2\text{NH}} \text{O}_2\text{N}^\text{CH}_3 \text{H}_2\text{Cl} \xrightarrow{\text{O}_2\text{N}^\text{CH}_3} \text{I} \]

\[ \text{CH}_2\text{N}\text{R}_2\text{NR}_2 \xrightarrow{\text{I}_2\text{HR}_2} \text{II} \]

\[ \begin{align*}
\text{Ar} \xrightarrow{\text{H}_2\text{C}^\text{CH}_2} \text{III} & \quad \text{Ar} \xrightarrow{\text{H}_2\text{C}^\text{CH}_2} \text{IV} \\
\text{H}_2\text{C}^\text{CH}_2 & \xrightarrow{\text{O}_2\text{N}^\text{CH}_3} \text{V} \quad \text{IV} \xrightarrow{\text{HO}} \text{VI}
\end{align*} \]

\text{CHART II}

The 5-methyl group in the title compound is greatly activated by virtue of its situation attached to a carbon in conjugation with the nitro group. Thus, it is found to undergo condensation with aldehydes readily forming styryl derivatives;\textsuperscript{11} it also undergoes a Michael-type addition with benzalacetophenone.\textsuperscript{12} Therefore, it must also be quite susceptible to the Mannich reaction, which has not so far been investigated.

The title compound, prepared by earlier reported methods,\textsuperscript{13} was treated in alcoholic solution with formalin and an amine (for the amines made use of, see table 1) at room temperature to yield the corresponding Mannich base (II) almost instantaneously. These have been found to be soluble in water and decomposed slowly on standing and readily when treated with acids into the parent isoxazole. Their U.V. spectra contained two maxima around 224 and 268 nm and were almost identical with the parent compound I, indicating no change in the basic chromophore. Their I.R. spectra contained all essential features of the isoxazole system,\textsuperscript{14} viz., bands at 1600, 1510, 1150 and 820 cm\textsuperscript{-1}. The observed additional frequencies at 880, 770 and 730 cm\textsuperscript{-1} are due to the additional methylenes introduced during the Mannich reaction. Their NMR spectra revealed signals at 1.8 \( \delta \) for the 3-methyl protons, 2.4 \( \delta \) for the methylene a-to the ring and 3.1 to 3.2 \( \delta \) for the rest of the methylenes. This data lends further support to the structural assignment II.