Alkaline Hydrolysis of 3-Methyl-4-nitro-5-styrylisoxazole with $Na^{18}OH$ (1)

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The use of enriched $Na^{18}OH$ in the hydrolysis of 3-methyl-4-nitro-5-styrylisoxazole leads to oxygen-labelled cinnamic acids. Isoxazole ring opening and cleavage of title compound has been investigated.

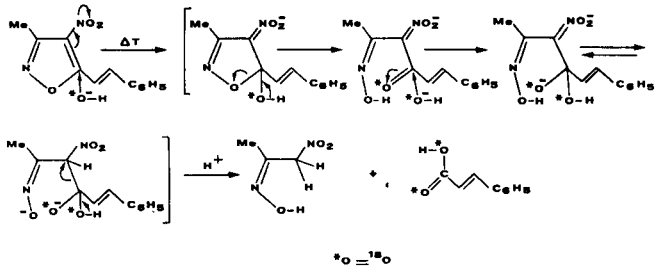
J. Heterocyclic Chem., **17**, 1643 (1980).

Sir:

In the recent years several isoxazole derivatives have been employed as starting materials for preparative purposes. In particular, various type of diketones were prepared by reduction of the requisite isoxazole derivatives (3-5).

During a study on the photoreactivity of 3-methyl-4-nitro-5-styrylisoxazole (I) it was found that cinnamic acid was prepared by treating I with sodium hydroxide, followed by acidification with hydrochloric acid (6). This reaction was then used to determine the structures of the dimers obtained from the photoreaction of I in the solid state (6) and in solution (7). In addition, substituted cinnamic acids were prepared with good yields by this route, using the appropriate 3-methyl-4-nitro-5-styrylisoxazoles (8). As an extension of the above behavior, we have now obtained acetic acid by refluxing an alkaline solution of 3,5-dimethyl-4-nitroisoxazole for 6 hours, followed by acidification with dilute hydrochloric acid (ir of *p*-bromophenacyl derivative superimposable with that of an authentic sample). The above results suggest that the 3-methyl-4-nitro-5-isoxazolyl group may be considered as a "masked" carboxyl group, the C-5 in the isoxazole being the carbon atom of the carboxyl resulting by alkaline hydrolysis of 3-methyl-4-nitro-5-alkyl-(or aryl)-isoxazole followed by acidification.

Quilico and Musante (9) explained the solubility of 3,5-dimethyl-4-nitro-isoxazole in alkali with the 1,5-ring opening, leading to the monoxime of 3-nitro-2,4-pentandione, which on acidification gave back the starting compound. If this was the case, both oxygen atoms in the carboxyl group of the cinnamic acid obtained from I should be those derived from the alkaline medium and not from the isoxazole ring. This behaiour is now demonstrated by using enriched $Na^{18}OH$, prepared by careful addition, in small portions, of sodium (90 mg.) to 20% $H^{18}OH$ (2 ml.). Compound I (155 mg.) was then added to the alkaline solution and refluxed for 6 hours. The unreacted I (33 mg.) was filtered off and the solution acidified with hydrogen chloride gas to give a solid which was filtered, dried and purified by sublimation (108°, 0.1 mm/Hg). The mass spectrum of this solid shows peaks at m/e 147, 148, 149, 150, 151 and 152. While the first two values may be correlated to the cinnamic acid obtained from the action of $Na^{16}OH$ present in the alkaline solution, those at m/e 151 and 152 correspond to $M^+ - 1$ and M^+ of the expected C_6H_5-CH=CH-$C^{18}O^{18}OH$. Signals at m/e 149 and 150 were attributable to $M^+ - 1$ and M^+ of mono-labelled oxygen cinnamic acid. These findings confirm that the alkaline hydrolysis of I occurs by nucleophilic attack of two hydroxide ions of the alkaline medium on C-5, according to the following scheme (10).



In addition we checked if, in the conditions used, it could be possible to have ^{18}O exchange between the above solution and unlabelled oxygen atoms of cinnamic acid. For this purpose a solution of enriched $Na^{18}OH$ (1 ml.) prepared as described, was added to cinnamic acid (50 mg.) and refluxed for 6 hours. After cooling, the mixture was filtered and the solution, acidified with hydrogen chloride gas gave a solid which was purified as described above. The mass spectrum of this product had the same peaks as those of cinnamic acid; in particular peaks at m/e 151 and 152 were absent.

The above findings, besides giving evidence for the isoxazole ring opening followed by cleavage of I, suggest that this reaction is a good route for the preparation of carboxylic acids with two ^{18}O-labelled in the carboxyl group.

REFERENCES AND NOTES

(1) Part of this work has been sent for the poster section to the XII Congresso Nazionale di Chimica Organica, S.C.I., Ancona (1980).

(2) Centro di Spettrometria di Massa e Analisi Frammentografiche,

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(10) Nitroacetonoxime reported in the scheme was not isolated.