Decomposition of Isoxazoles and of 1-Azirines by Aromatic Amines. Formation of Urea

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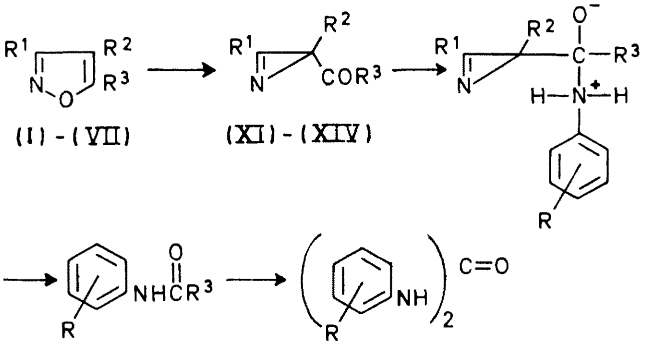
Summary 3-Substituted or 3,4-disubstituted 5-amino- and 5-alkylthio-isoxazoles decompose into ureas on treatment with aromatic amine, the intermediacy of 1-azirines in this decomposition being demonstrated.

BASE-INDUCED ring opening of 3-mono- or 5-mono-substituted isoxazoles has been well studied, their transformation into nitriles being the usual reaction.[1] 3,5-Disubstituted and 3,4,5-trisubstituted isoxazoles are generally stable towards base. During studies on the thermally-induced valence isomerization of isoxazoles into 1-azirines,[2] it was found that 3-substituted and 3,4-disubstituted 5-amino- and 5-alkylthio-isoxazoles react with aromatic amines in a specific manner. The reaction with aniline appears to be very selective with respect to the structure of these isoxazoles, while the reaction with *o*-toluidine and *o*-chloroaniline follows a common decomposition process.

For example, on heating a solution of 5-amino-3-phenylisoxazole (I) (0·26 molar) in refluxing *o*-toluidine for a few hours a compound with m.p. 247° was isolated as the major product. This compound was identified as *NN'*-di-*o*-tolylurea (VIII).† The yield of (VIII) from other 5-aminoisoxazoles [(II; $R^1 = Ph$, $R^2 = Me$, $R^3 = NH_2$); (III; $R^1 = Ph$, $R^2 = Br$, $R^3 = NH_2$); (IV; $R^1 = Bu^n$, $R^2 = Pr^n$, $R^3 = NH_2$)] was 30—47%, while that from 5-alkylthioisoxazoles [(V; $R^1 = Ph$, $R^2 = H$, $R^3 = SMe$); (VI; $R^1 = Ph$, $R^2 = H$, $R^3 = SBu^n$); (VII; $R^1 = Ph$, $R^2 = H$, $R^3 = SCH_2Ph$) was 13—23%. These results show the reaction to be independent of the nature of the substituents at C-3 and C-4. The reactions of 5-alkylthioisoxazoles and of 5-amino-4-halogenoisoxazoles are quite rapid compared with those of 5-alkoxyisoxazoles, from which the urea (VIII) was obtained in less than 6% yield despite prolonged heating. During the reaction ammonia and/or thiol is formed, while ammonium halide, together with (VIII), is produced from 5-amino-4-halogenoisoxazoles.

Although the reactions of these isoxazoles with *o*-chloroaniline proceed satisfactorily, giving *NN'*-di-*o*-chlorophenylurea (IX) (m.p. 233°)† in 30—40% yield, treatment of (I) and (VII) with aniline does not yield *NN'*-diphenylurea (X) in a detectable amount in spite of the evolution of ammonia or thiol during heating, the isoxazole (IV) being the only one that produced the urea (X) (m.p. 236°)† in useful yield.



(I) - (VII) (XI) - (XIV)

(VIII) - (X)

It is suggested that the reaction leading to the ureas proceeds *via* 1-azirines, isomeric with the starting isoxazoles, the formation of which is quite reasonable in high-boiling dilute solution in the light of our studies,[2c] although in the present case the cleavage of an N–O linkage is not necessarily triggered by homolysis alone. Nucleophilic attack on amide or thiolester group by amine gives the final product by way of *N*-arylcarbamide or *N*-arylthiolcarbamate. This suggestion is experimentally proved by independent reactions of 2-aryl-3-carbamoyl-1-azirines (XI; $R^1 = Ph$, $R^2 = H$, $R^3 = NH_2$);[2c] (XII; $R^1 = p\text{-}MeC_6H_4$, $R^2 = H$, $R^3 = NH_2$);[2c] and (XIII; $R^1 = Ph$, $R^2 = Me$, $R^3 = NH_2$) (m.p. 110—111°) [prepared from (II) more favourably in refluxing tetralin than by the photochemical method] with *o*-toluidine and *o*-chloroaniline, the azirines (XI) and (XIII) being the valence isomers of (I) and (II), respectively. In each reaction the ureas (VIII) and (IX) were produced as the major products in 30—45% yield with concomitant evolution of ammonia. On the other hand, the reaction of 3-methoxycarbonyl-1-azirine (XIV) ($R^1{=}p\text{-}ClC_6H_4$, $R^2{=}H$, $R^3{=}CO_2Me$)[2b] with *o*-toluidine is complicated, the urea (VIII) being isolated in negligible yield (< 1%), and this result is also compatible with the results for 5-alkoxyisoxazoles.

It is stated that if the reaction is carried out in dilute solution, 2-imidazolone[3] and 3,6-dicarbamoylpyrazine,[2c] which are the products from neat-melt reactions of the present 5-aminoisoxazoles and 3-carbamoyl-1-azirines, are not formed at all, but in concentrated solution these compounds become the major products. For example, an *o*-toluidine solution of (I) (2·7 molar) gives 3,6-dicarbamoyl-2,5-diphenylpyrazine as the only isolable product (25% yield). However, the intermediacy of these 2-imidazolones and pyrazines in the formation of the ureas is ruled out.

The present results provide a novel entry into the little studied amine-induced reaction of 1-azirines,[4] and, in addition, into amide chemistry, because the one-step formation of a urea from a carboxamide is a novel reaction in itself.

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† All structures are based on analyses, i.r. and u.v. spectrometry, and/or comparison with an authentic sample.

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