# THE MECHANISM OF THE ALKYLATION OF ISOXAZOLIDIN-3-ONE

A. D. Voitenko, Ya. A. Kastron,
and S. A. Hiller

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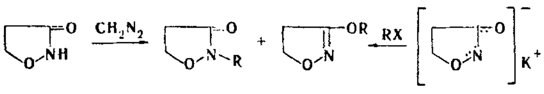
In solvents of different polarities, the lactam–lactim tautomeric equilibrium of isoxazolidin-3-one is strongly displaced in the direction of the lactam. The lactim form cannot be detected. It has been concluded that there is no connection between the dual chemical behavior of isoxazolidin-3-one and its potassium salt in the alkylation reaction with the equilibrium isomerization of these compounds. It has been shown that the mechanism of alkylation is connected with the structure of the lactam anion. Evidence is given in favor of a mesomeric structure of the anion with the main charge on the nitrogen at which substitution chiefly takes place.

In organic chemistry in recent years there has been an intensive study of problems connected with tautomerism, including that of heterocycles with a nitrogen-containing grouping in the tautomeric system.

The object of our investigation is isoxazolidin-3-one (I), potentially tautomeric because of the presence of an amide group in the molecule. The present paper is devoted to a discussion of the routes and mechanism of the alkylation of (I) and its potassium salt (II), the results of which we have reported previously [1]. As has been shown, the reaction leads to the formation of a mixture of derivatives of both tautomeric (lactam and lactim) forms of (I) with a predominance of the N-alkylated isomer:



I III–VII a III–VII b II

III $R=CH_3$; IV $R=C_2H_5$; V $R=C_3H_7$; VI $R=i\text{-}C_3H_7$; VII $R=CH_2-\underset{\diagdown O \diagup}{CH-CH_2}$; $X=Cl, Br$

An analysis of the possible routes for this reaction led us to the necessity for investigating the connection of the observed dual reactivity with the tautomerism of the initial compounds, since tautomerism is one of the main causes of dual reaction. Information on the state of the tautomeric equilibrium of (I) and (II) in solutions, which was lacking in the literature, could not be obtained by means of the electronic spectra, since these are poorly characteristic for the heterocyclic system under investigation because of the absence of a conjugated system of bonds. The UV spectra of the ketonic, enolic, and anionic forms of (I) in solvents of different polarities have absorption maxima close to 220 nm with some differences in intensity [for (I-VII), ε 3300-3800*].

We obtained additional information on the tautomeric equilibrium of (I) in solutions with the aid of IR spectroscopy* (see Fig. 1). As was to be expected, in water (spectrum taken in $D_2O$) (I) exists in the

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*The UV spectra were taken on an SF-4A instrument in water, ethanol, and n-hexane (c $10^{-3}$-$10^{-4}$ M); and the IR spectra on a UR-20 instrument (c $10^{-1}$ M).

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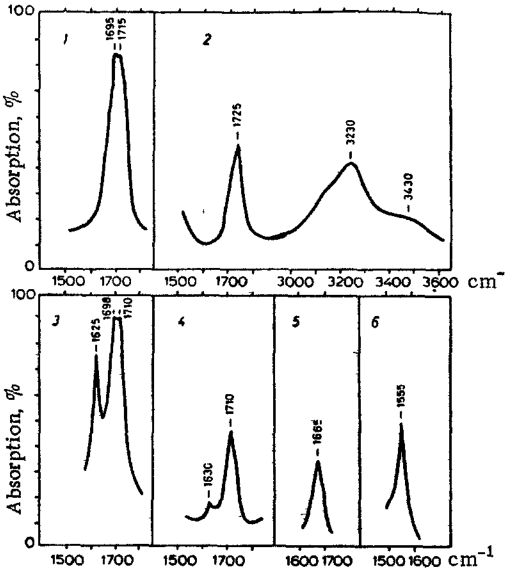

Fig. 1. IR spectrum: (I) in chloroform (1), dioxane (2), and $D_2O$ (5); (VII) as a liquid film (3) and in dioxane (4); (II) in $D_2O$ (6).

lactam form, as is shown by a strong carbonyl band at 1665 cm$^{-1}$; no absorption is observed in the region of the stretching vibrations of the azomethine bond.

Since with a decrease in the polarity of the solvent the equilibrium is shifted in the direction of enolization, we took the IR spectrum of (I) in dioxane, but this did not show the presence of the lactim form of (I) in the solution. This was indicated by the absence of the absorption of a C=N bond and also by an analysis of the region of the spectrum above 3000 cm$^{-1}$: since in dioxane we have the spectrum of the free lactam, as will be shown below, this readily permits a secondary amino group to be distinguished from a hydroxy group. In this spectrum, a band with its maximum at 3230 cm$^{-1}$ is due to the $\nu_{N-H}$ stretching vibrations, while absorption in the 3600-cm$^{-1}$ region characteristic for a free hydroxy group is absent. In the 3430-cm$^{-1}$ region an overtone of the carbonyl group appears in the form of the broad band of medium intensity [2, 3].

The results obtained show a pronounced shift of the tautomeric equilibrium of (I) in solvents of different polarities in the direction of the lactam form. The results of the methylation of (I) with diazomethane do not correlate with this conclusion and therefore the dual reactivity observed in the reactions of (I) is not connected with tautomerism: both isomers (IIIa and IIIb) are produced from the lactam form of (I). We may note, in passing, that methylation with diazomethane involves the dissociation of the initial compound with the formation of a proton and an anion [4, 5].

Incidentally, in working with the IR spectra we were able to establish the reason for the split nature of the carbonyl band in (I) and its alkyl derivatives, which was mentioned in the preceding paper [1]. It was reported there that the splitting of the carbonyl maximum is retained when the spectrum is recorded in Nujol, in a KBr tablet, and in chloroform. However, in the IR spectra of dioxane solutions of the compounds (see Fig. 1) the carbonyl band has only one maximum. The cause of the observed splitting is the considerable tendency of the compounds considered to the formation of intermolecular hydrogen bonds. The splitting of the maximum in the spectrum is due to the presence of both free and associated forms. As can be seen from the IR spectra, intermolecular association is retained partially even in the feebly polar chloroform. In practice, the band of a carbonyl group not participating in the formation of a hydrogen bond is observed only in dioxane.

Compound (II), which we also used in the alkylation reaction, has the lactim structure according to Vinokurov et al. [6], as is confirmed by the absence of a carbonyl band in its IR spectrum. However, the assignment made by these authors [6] of the band at 1560 cm$^{-1}$ in the spectrum of (II) to the stretching vibrations of the C=N bond appears to us to be doubtful, since in the IR spectrum of the products of the alkylation of (I) (III-VII), containing, according to PMR, from 4 to 37% of the O-substituted isomer, there is only an absorption band close to 1630 cm$^{-1}$, which we assign to the azomethine bond C=N of the lactim form of (I) [1]. It follows from what has been said that the lactim structure of (II) in the solid state cannot be considered as having been strictly demonstrated.

Leaving for the moment the question of the true structure of (II), it can be said concerning its state of tautomeric equilibrium that under the conditions of the alkylation reaction (ethanol) the undissociated form of the compound exists in insignificant amount, as is shown by a determination of the degree of dissociation of (II) in absolute ethanol which we performed specially (for a 0.001 N solution, $\alpha = 0.96$). Furthermore, tautomerism of (II) due to different positions of the metal atom in the molecule is fundamentally impossible because of the ionic nature of the compound.

Thus, as in the case of compound (I), the dual chemical behavior (II) is due not to tautomerism but to other factors. We link the results of the alkylation of (I) and (II) primarily with the structure of the lactam anion, the formation of this being a preliminary stage of the reaction in both cases. In spite of the relatively acidic nature of (I) ($pK_a$ 6.80), its IR spectrum in $D_2O$ gives no information on the structure of the lactam anion because of the insufficient concentration of the latter in the solution ($\sim 10^{-4}$ g-ion/liter). At the same time, because of the salt-like nature of the compound, the spectrum of (II) in $D_2O$ is precisely the spectrum of the anion of interest to us. As can be seen from Fig. 1, both the carbonyl band and the absorption of the azomethine bond in the 1630-$cm^{-1}$ region are absent from the anion under investigation, but there is a band at 1560 $cm^{-1}$ the presence of which in the spectrum of solid (II) has been mentioned above. The considerable similarity of the IR spectra of the solid substance and of a solution of (II) leads to the idea of a structure of the anion of the compound which is similar for both states. Judging from the absence of absorption at 1630 $cm^{-1}$, the anion under consideration does not have a strictly fixed $C{=}N$ double bond, and its charge is distributed between the nitrogen and oxygen atoms of the amide group. This becomes the more understandable if account is taken of the mesomeric effect of the oxygen heteroatom, as a consequence of which there is a decrease in the difference in nucleophilicity existing between the N and O atoms and, in the final account, a more uniform distribution of the electron density between them. A confirmation of this is precisely the band at 1560 $cm^{-1}$ that is present in both spectra and which we have assigned to the asymmetric stretching vibrations of $C{=}O$ and in the $-N{=}C{=}O$ grouping by analogy with $O{=}C{=}O$ in the carboxylates [2, 3]. There is nothing unusual in the fact that the negative charge of the anion is not fixed on the oxygen but is distributed between the nitrogen and the oxygen and is even, perhaps, largely concentrated on the nitrogen, since just such a structure has been shown for a number of anions of cyclic amides [7]. This feature is characteristic for the anions of amides in which the lactam form makes the main contribution to the basic structure of the amide.

According to Gompper [4, 5], an analysis of the IR spectrum of the free lactam is extremely useful for determining the distribution of the electron density in a lactam anion: the high carbonyl frequency in the spectrum of (I) in dioxane ($\nu_{C=O} = 1725$ $cm^{-1}$) shows precisely, in the final account, a high electron density on the nitrogen atom of the anion and, consequently, a tendency of compounds dissociating with the formation of such an anion to undergo N-substitution reactions, as is actually the case for (I) and (II). Since in the alkylation of compounds (I) and (II) an anion takes part in which the main nucleophilic center is a nitrogen atom, it is this atom at which substitution mainly takes place. The formation of greater or smaller amounts of the O-substituted isomer in the alkylation of (I) or (II) takes place because of the presence in the ion of an additional nucleophilic center on the oxygen. The difference in the amounts of O-substituted derivatives formed is due to differences in the structures of the hydrocarbon radical of the alkyl halides, namely: with an increase in the length and with the branching of the carbon chain of the latter the amount of O-alkylated isomer increases.

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