α-SUBSTITUTED α-AMINO ACIDS

COMMUNICATION 5. METHODS OF PREPARATION OF SUBSTITUTED α,α-DIAMINO-CARBOXYLIC ACIDS

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The α,α-diaminocarboxylic acids have been either difficultly accessible or totally inaccessible substances up to the present time. Only the representatives of the group of N,N'-diacyl derivatives of these compounds could have been readily prepared by the action of acid amides or corresponding nitriles on α-keto acids [1-13] (for exceptions see [4, 8, 9, 14, 15]). Several other methods of preparation described in the literature for the preparation of derivatives of α,α-diamino carboxylic acids (specifically, β-halo-substituted ones) have been used so far only for the synthesis of individual representatives of these compounds [4, 8, 16-19].

We considered that the path of introduction of various substituents into the α-position of α-amino acids through oxazolinones (II) and 4-bromo-oxazolinones (III), which was recently suggested by us [20-23], could also be used for the introduction of a second amino group into their molecules. It actually turned out that this route readily permits one to prepare various α,α-diamino acids in the form of their derivatives and thus many of these substances have become quite accessible compounds.

\[
\begin{align*}
&\text{HCR} - \text{COOH} &\quad\text{Ac}_2\text{O} &\quad\text{HCR} - \text{CO} \quad\text{Br}_2 \\
&\text{NHCOC}_6\text{H}_5 &\quad\text{(I)} &\quad\text{N} = \text{C} - \text{C}_6\text{H}_5 &\quad\text{(II)} &\quad\text{N} = \text{C} - \text{C}_6\text{H}_5 &\quad\text{(III)} \\
&\text{R}^\prime\text{R}''\text{N} - \text{CR} - \text{COOR}'' &\quad\text{R}^\prime\text{R}''\text{NH} &\quad\text{BrCR} - \text{COOR}'' &\quad\text{R}^\prime\text{R}''\text{N} - \text{CR} - \text{CONR}^\prime\text{R}'' \\
&\text{NHCOC}_6\text{H}_5 &\quad\text{(V)} &\quad\text{NHCOC}_6\text{H}_5 &\quad\text{(IV)} \\
\end{align*}
\]

It was established that if the amine, used for the reaction (for example: aniline, benzylamine, piperidine) reacts sufficiently rapidly with the oxazolinone ring, then one can use this amine to act directly on the intermediate bromooxazolinone (III), thereby obtaining in a number of cases the corresponding amides of α-amino-α-acylaminocarboxylic acids of type (IV) in sufficiently high yields. See scheme (I) → (II) → (III) → (IV), and Tables 1 and 2.

However, if the amine that is used (dibenzyamine, dibutylamine, and others) opens the oxazolinone ring slowly, side reactions are observed (polymerization, tar formation), which lead to a decline in the yield of the final product (IV) and, at times, the latter cannot be isolated in the individual state (see Table 1). In such cases, the ability of the amines to open the oxazolinone ring was studied in the example of 2-phenyl-5-oxazolinone.
## Table 1

<table>
<thead>
<tr>
<th>Amine</th>
<th>Reaction with 2-phenyl-5-oxazolinone</th>
<th>Reaction with 4-bromo-2-phenyl-5-oxazolinone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conditions of the reaction</td>
<td>Yield of amide of hippuric acid, in %</td>
</tr>
<tr>
<td>Aniline</td>
<td>25°; 10 min (in dichloroethane medium)</td>
<td>98</td>
</tr>
<tr>
<td>Benzylamine</td>
<td>Same</td>
<td>94</td>
</tr>
<tr>
<td>Piperidine</td>
<td>Same</td>
<td>60</td>
</tr>
<tr>
<td>Dibenzytaminate</td>
<td>Same</td>
<td>23</td>
</tr>
<tr>
<td>Dibutylamine</td>
<td>Same</td>
<td>0</td>
</tr>
<tr>
<td>Diisoamylamine</td>
<td>Same</td>
<td>0</td>
</tr>
</tbody>
</table>

It is necessary to open the oxazolinone ring by means of some other reagent, prior to the reaction with the amine. Thus, by acting on the intermediate bromooxazolinone (III) with one mole of some alcohol, (or a mercaptan), at first and only then with the amine, it is possible to synthesize in satisfactory yields the corresponding esters of α-amino-α-acylaminoacetic acid (VI). It is natural to assume that these compounds can be prepared also with the same amines (aniline, benzylamine, piperidine and others) which are applicable to the synthesis of amides of type (IV). See scheme (I)→(II)→(III)→(V)→(VI) and Table 2.

It should be noted that in some cases this reaction is accompanied by secondary transformations. For example, in the reaction of bromooxazolinone (III, R=H) first with methyl or benzyl alcohol, followed by α-amino-pyridine, the compound of type (VI), which is first formed, cyclizes as a result of an intramolecular cleavage of alcohol and forms compounds (VII) (compare [24, 25]).

![VII](image)

There is one more possible synthesis of substituted α,α-diaminocarboxylic acids; it was clarified by us in the process of a study of the properties of α-hydroxy-α-acylamino acids (VIII). It was shown that the latter substances are capable of transforming, on being heated with acid amides, into α,α-bis-(acylamino) acids (IX), some representatives of which (see Table 2) were indeed synthesized in this manner:

![OH](image)

(VIII) → (IX)