SYNTHESIS AND PROPERTIES
OF 2-OXOOXAZOLOPYRIDINES
(REVIEW)

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Published data on the synthesis and properties of 2(3H)-oxooxazolo[4,5-b]-, 2(1H)-oxooxazolo[5,4-b]-, and 2(3H)-oxooxazolo[4,5-c]pyridines up to 1997 are reviewed.

Compared with other condensed systems of the pyridine series the derivatives of 2-oxooxazolopyridines have been studied not enough. Interest in these compounds has increased more and more in recent years, since substances exhibiting a wide spectrum of biological activity have been found among them.

Among the derivatives of 1(3H)-oxooxazolo[4,5-b]pyridines there were substances that exhibited analgesic [1-10] and antiinflammatory [8, 9] activity. Some derivatives were depressants of the central system [8]. The thiophosphates of 2(3H)-oxooxazolo[4,5-b]pyridines were characterized by high insecticidal, acaricidal, and antihelminthic [10-24] activity.

The derivatives of 2(1H)-oxooxazolo[5,4-b]pyridines included compounds that exhibited antiinflammatory [25] and analgesic [25-27] activity.

Data on the synthesis and properties of 2-oxooxazolopyridines have not been reviewed in the literature. We set ourselves the task of classifying the published data on this extremely interesting group of heterocyclic substances.

1. SYNTHESES OF 2-OXOOXAZOLOPYRIDINES

The isomeric forms (I-IV) are possible for 2-oxooxazolopyridines:

![Chemical structures]

The methods of synthesis and characteristics have been studied most widely for the derivatives of 2(3H)-oxooxazolo[4,5-b]pyridine (I). The derivatives of 2(1H)-oxooxazolo[5,4-b]pyridine (II) and 2(3H)-oxooxazolo[5,4-c]pyridine (III) have been studied less, and there are no published data on 2(1H)-oxooxazolo[5,4-c]pyridine (IV).

1.1.1. Carbonylation of 2-Amino-3-hydroxypyridines. Several reagents have been proposed for carbonylation: phosgene [8, 11-14, 16, 23, 28-32], carbonyldiimidazole [2, 3, 7, 28, 29, 33], disuccinimidocarbonate [34], S,S'-bis[1-phenyl-(1H)-tetrazol-5-yl] dithiocarbonate [35, 36], carbon monoxide under pressure in the presence of selenium [37, 38], and urea [39].

If 2-amino-3-hydroxypyridine (V) (X = H) is heated with phosgene in pyridine, oxazolopyridine (I) is formed with a yield of 95% [11, 28]. The corresponding 6-methylpyridine reacts similarly [13]. With the less toxic carbonyldiimidazole in THF a smaller yield (75-77%) of compound (I) was obtained [2].

\[
\begin{align*}
V & \xrightarrow{\text{COCI}_2} I \\
V & \xrightarrow{\text{S,S'-bis[1-phenyl-(1H)-tetrazol-5-yl] dithiocarbonate}} \text{VI} \\
V & \xrightarrow{\text{S,S'-bis[1-phenyl-(1H)-tetrazol-5-yl] dithiocarbonate}} \text{I} + \text{HS}_2\text{N} & \text{N} & \text{N} & \text{N}
\end{align*}
\]

The action of S,S'-bis[1-phenyl-(1H)-tetrazol-5-yl] dithiocarbonate on the pyridine (V) even at room temperature leads to the required condensed system (I) through the intermediate formation of compound (VI) [35].

1.1.2. Intramolecular Cyclization of 3-Hydroxy-2-pyridylureas and Urethanes. When N-(3-hydroxy-2-pyridyl)ureas (VII) are heated in inert solvents, intramolecular cyclization with the elimination of the amine occurs, and oxooxazolopyridine (I) is formed [30].

\[
\begin{align*}
\text{VII} & \xrightarrow{\Delta} \text{I} + \text{R}^1\text{RNH} \\
R, R^1 & = \text{alkyl}
\end{align*}
\]

2(3H)-Oxooxazolo[4,5-b]pyridine (I) is obtained with 62% yield [30] under refluxing of compound (V) with a twofold excess of butyl isocyanate in toluene without isolation of the urea (VIII) that forms.

\[
\begin{align*}
V + 2\text{BuNCO} & \xrightarrow{\Delta} \text{I} + \text{(BuNH)}_2\text{CO} \\
V & \xrightarrow{\Delta} \text{I} + \text{(BuNH)}_2\text{CO}
\end{align*}
\]

When heated at 200°C in diphenyl ether 3-hydroxy-2-ethoxycarbonylaminopyridine (IX) undergoes cyclization to oxooxazolopyridine (I) [40].