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Ring Opening Reactions: Synthesis of AICAR Analogs as Potential Antimetabolite Agents

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RING OPENING REACTIONS: SYNTHESIS OF AICAR ANALOGS AS POTENTIAL ANTIMETABOLITE AGENTS

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In an attempt to improve the A_{2A} selectivity of the 2-(aryl)alkylthio derivatives of adenosine, we planned the synthesis of the corresponding derivatives of the 5'-N-ethylcarboxamidoadenosine (NECA). For this purpose, we designed the synthesis of 2-mercapto-NECA to be pursued by means of an opening-closure method. We obtained the open AICAR analog; however, ring closure efforts failed to give the desired compound. The newly synthesized AICAR derivative could potentially be endowed with antiviral or antitumoral activity.

INTRODUCTION

Derivatives of adenosine substituted at the C2 position of the purine ring with (aryl)alkylthio groups have been reported to possess coronary vasodilating activity and platelet aggregation inhibitory activity, probably due to their interaction with the adenosine $A_{\rm 2A}$ receptors. [1–4]

In an attempt to improve the A_{2A} selectivity of the 2-(aryl)alkylthio derivatives of adenosine, since the substitution of the 4'-hydroxymethyl group with an N-ethylcarboxamido substituent usually increased A_2 vs. A_1 binding affinity, [5-7] we planned the synthesis of the corresponding derivatives of the 5'-N-ethylcarboxamidoadenosine (NECA).

In 1975, Kikugawa and Suehiro^[8] reported the synthesis of 2-mercaptoadenosine by the "opening-closure" method and its successive reaction with various 2-(aryl)alkylbromides to obtain the corresponding 2-(aryl)alkylthio derivatives of adenosine. Following a similar scheme, we designed the synthesis of 2-mercapto-NECA, which could have been reacted with (aryl)alkylbromides to obtain the desired compounds.

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 $\begin{tabular}{ll} \textbf{SCHEME 1} & Preparation of AICAR analog 4. \end{tabular}$

For this purpose, the 4'-hydroxymethyl group of the commercially available 2'-3'-isopropilideneadenosine was oxidized to carboxylic acid to obtain compound 1, which was reacted with m-chloroperbenzoic acid in order to form an N-oxide at the N1 position of the purine ring (2). After deprotection of compound 2 by treatment with HC1 in dioxane, the obtained compound 3 was refluxed with NaOH to open the purine ring giving the AICAR analog 4 in low yield (Scheme 1), whose identity has been confirmed by means of ¹H-NMR spectroscopy and mass spectrometry.

In order to confirm the structure of compound **4** and to overcome the difficulties in handling carboxylic acids, compound **1** was converted to the corresponding N-ethylcarboxamido derivative **5**, which was then deprotected to obtain NECA. The latter was treated with m-Cl-perbenzoic acid and the resulting N-oxide derivative was refluxed with NaOH yielding compound **4** (Scheme 1).

The second route proved to be preferable both in terms of total yield and easiness of handling.

In a search for an alternate and shorter synthetic route, an attempt to open the isopropylidene protected nucleoside **2** resulted in the elimination of the 3'-hydroxyl group and in the formation of a C3'-C4'-double bond (Scheme 2). The structure of the obtained compound **8** has been confirmed by means of ¹H-NMR spectroscopy.

Compound 4 was treated with CS_2 under different reaction conditions, in an attempt to obtain a closed purine ring bearing a mercapto group at the $\mathrm{C2}$ position. The resulting compound would have been treated with ethylamine to give the desired 2-mercapto derivative of NECA. However, these ring closure efforts failed to give the desired compound.

In order to overcome these problems, we synthesized the wanted 2-(aryl) alkylthio derivatives of NECA by reacting 2-iodoNECA with the appropriate mercaptans, as reported elsewhere.^[9]

In conclusion, the above described reactions yielded new AICAR analogs, which will be tested for their antiviral and antitumor activity, and can constitute the starting point for further modifications of AICAR.

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