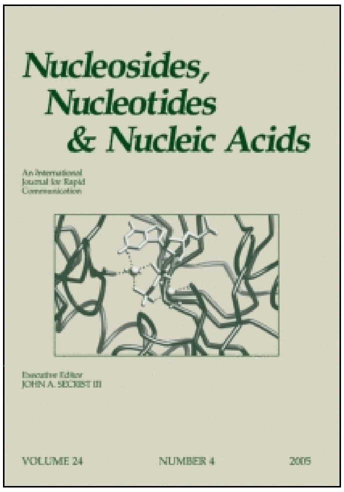

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Reaction of Acetylenic Compounds With Nucleobases in Nucleosides, Nucleotides and Poly(A)

M. Olomucki[a]; J. Y. Le Gall[a]; P. Roques[a]; F. Blois[a]; S. Colinart[a]
[a] Laboratoire de Biochimie Cellulaire, Collège de France, Paris, Cedex 05

To cite this Article Olomucki, M. , Gall, J. Y. Le , Roques, P. , Blois, F. and Colinart, S.(1985) 'Reaction of Acetylenic Compounds With Nucleobases in Nucleosides, Nucleotides and Poly(A)', Nucleosides, Nucleotides and Nucleic Acids, 4: 1, 161 — 163

To link to this Article: DOI: 10.1080/07328318508077844

URL: http://dx.doi.org/10.1080/07328318508077844

NUCLEOSIDES & NUCLEOTIDES, 4(1&2), 161-163 (1985)

REACTION OF ACETYLENIC COMPOUNDS WITH NUCLEOBASES IN NUCLEOSIDES, NUCLEOTIDES AND POLY(A)

M. Olomucki*, J.Y. Le Gall, P. Roques,
F. Blois and S. Colinart

Laboratoire de Biochimie Cellulaire, Collège de France,
11, pl. Marcelin Berthelot, 75231 Paris Cedex 05

Summary : α-Acetylenic esters react with the NH_2 group and the adjacent ring nitrogen of adenosine, cytidine, adenine nucleotides and poly(A) by addition across the triple bond and formation of a lactam with the ester group.

Earlier works from this laboratory have shown that chlorotetrolic (4-chloro-2-butynoic) esters[1], $ClCH_2$-C≡C-COOR, react under mild conditions with protein nucleophiles by addition across the triple bond and substitution of chlorine and can thus be used as bifunctional protein reagents[2].

More recently we have found that these esters can also react with nucleic acids bases ; in this case, however, the double reaction involves, in addition to the triple bond, the ester group instead of the chlorine[3]. Thus, when adenosine is treated at room temperature with a chlorotetrolic ester in hydroalcoholic solution of apparent pH 4 - 5, compound 1a is obtained in good yield. The primary attack consists in addition of the N^1 atom of adenine across the triple bond, leading to an ethylene intermediate of the Z form in which the ester function reacts with the NH_2 group to give a lactam. If the reaction is carried out in neutral pH, the roles of the two nitrogens are reversed and the isomeric compound 2a is formed.

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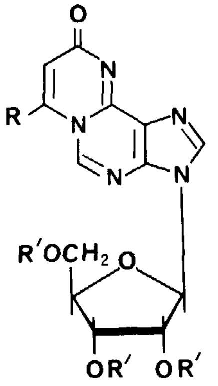

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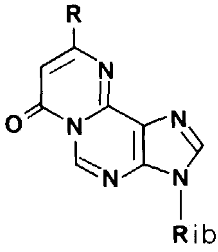

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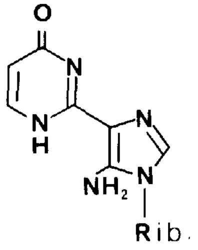

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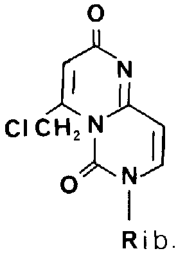

4

a, R = $ClCH_2$, R' = H

b, R = $ClCH_2$, R' = Ac

c, R = R' = H

a, R = $ClCH_2$

b, R = ICH_2

The properties of the two isomers are quite different. Compound 1a is sparingly soluble in water and in most organic solvents, while 2a has a better solubility ; the derivative 1b, prepared by reaction of methyl chlorotetrolate with 2',3',5'-triacetyladenosine, is much more soluble than 1a. The chloromethyl group is more reactive in 1a than in 2a. In contrast to derivatives of the 1 type, 2a and its iodo analogue 2b (obtained from 2a by the Finkelstein reaction) are photolabile and fluorescent, although the quantum yield (0.05) and the fluorescence lifetime (2.5 nsec) are low.

Reaction of adenosine with ethyl propiolate leads to compound 1c. On heating, the latter is converted to 3 in high yield.

Cytidine also reacts with chlorotetrolic esters to give the pyrimido-pyrimidine 4. Guanosine does not react, at least under the usual mild experimental conditions.

Treatment of adenine nucleotides with methyl chlorotetrolate in neutral pH leads to the corresponding derivatives having a structure of the 2 type. Preliminary tests of enzymic activity have shown that adenylate kinase is active with modified ATP but not with modified AMP, pyruvate kinase is active with modified ADP and the ATP derivative inhibits lactate dehydrogenase.

This new derivatization of nucleobases was also extended to poly(A). The relationship between the rate of chemical modification and the conformation of the polymer was studied by circular dichroism and by measuring the melting temperatures of modified poly(A)-poly(U) complexes. Significant conformational changes of poly(A) occur when about 20 % of residues are modified.

Poly(A) modified to the extent of 5-10 % was covalently bound through its chloromethyl groups to thiolated polysaccharides and used for affinity chromatography of poly(U).

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