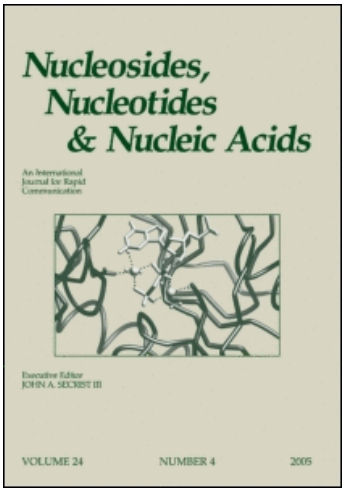


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Regioselective 2'-O Sugar Arylation in Adenine Nucleosides by The Elliptinium Agetate, An Antitumor Agent

G. Pratviel[a]; J. Bernadou[a]; B. Meunier[ab]; C. Paoletti[ab]
[a] Laboratoire de Pharmacologie et Toxicologie Fondamentales du CNRS, TOULOUSE [b] Laboratoire de Biochimie, Institut Gustave Roussy, VILLEJUIF

To cite this Article Pratviel, G. , Bernadou, J. , Meunier, B. and Paoletti, C.(1985) 'Regioselective 2'-O Sugar Arylation in Adenine Nucleosides by The Elliptinium Agetate, An Antitumor Agent', Nucleosides, Nucleotides and Nucleic Acids, 4: 1, 143 — 146
To link to this Article: DOI: 10.1080/07328318508077839
URL: http://dx.doi.org/10.1080/07328318508077839

NUCLEOSIDES & NUCLEOTIDES, 4(1&2), 143-146 (1985)

REGIOSELECTIVE 2'-O SUGAR ARYLATION IN ADENINE NUCLEOSIDES BY THE ELLIPTINIUM ACETATE, AN ANTITUMOR AGENT.

G. Pratviel[1], J. Bernadou[1], B. Meunier[1*] and C. Paoletti[2].

[1] Laboratoire de Pharmacologie et Toxicologie Fondamentales du CNRS, 205, route de Narbonne, 31400 TOULOUSE.

[2] Laboratoire de Biochimie, Institut Gustave Roussy, 16, avenue Paul Vaillant Couturier, 94800 VILLEJUIF.

Summary. The oxidized form of the antitumor agent elliptinium acetate is able to arylate the sugar moiety of various nucleosides. The presence of an hydroxy group in 2'-α position is strictly required for the formation of the elliptinium adducts. When no free hydroxy exists in 3'-α position uncyclised structures were obtained in contrast with spiro derivatives observed in the case of adenosine.

Elliptinium acetate 1 (9-OH-NME or N^2-methyl-9-hydroxyellipticinium acetate) behaves not only as an intercalating antitumor agent but also as a strong electrophile after a biooxidation process (2). Recently we have shown that ribonucleosides are regioselectively arylated by the quinone-imine form 2 of elliptinium acetate (3).

The main fact of the arylation procedure is the preliminary attack of the 2'-oxygen of the sugar on the electrophilic C_{10} atom of the quinone-imine 2. In adenosine, a secondary cyclisation occurs leading to a spiro derivative 5 (3,4). We report here evidences that final structures for 3'-O-methyl adenosine, cordycepin and xylofuranosyl adenine adducts are uncyclised ones, 3 or 4, depending on reducing or oxidizing conditions.

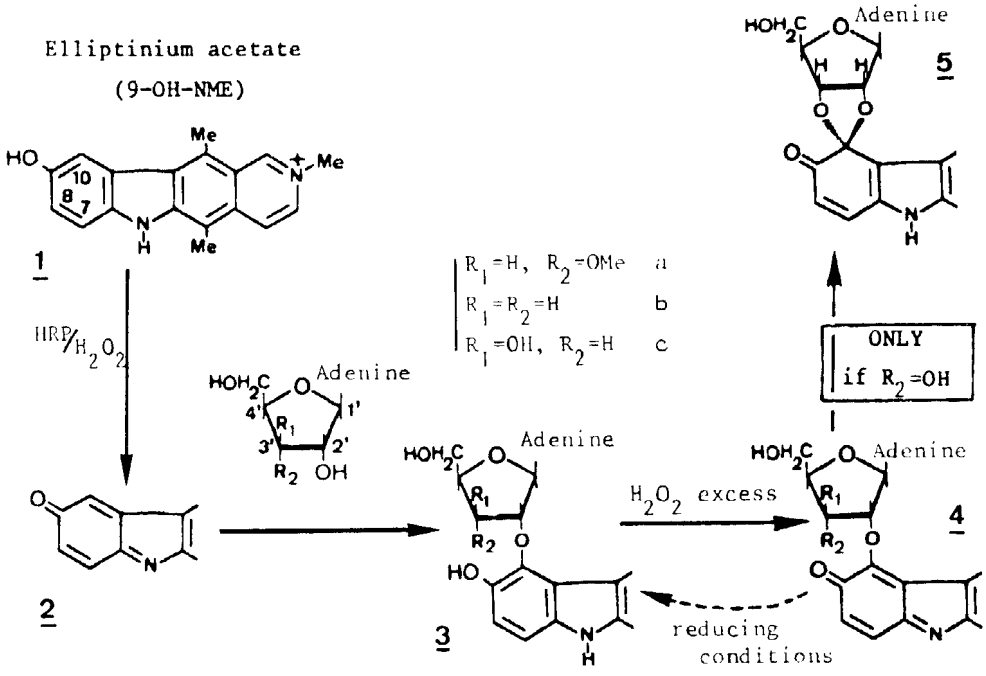
EXPERIMENTAL

Materials. The 9-OH-NME was a gift of SANOFI (France). Horse radish peroxidase (HRP), 3'-O-methyladenosine and cordycepin were purchased from Sigma. Xylofuranosyladenine was a gift of Pr. Imbach and Dr. Gosselin (Montpellier).

0732-8311/85/0401-0143$3.50/0

Synthesis. To 0.05 mmol of nucleoside, 0.01 mmol of 9-OH-NME and 100 µl of 10^{-4} M HRP in 100 ml of 1/15 M phosphate (pH 8) buffer, 200 µl of 10^{-1} M H_2O_2 was added in one fraction. The reaction lasted for 3 min at room temperature. For oxidized unstable compounds 4, only the cordycepin derivative 4b was isolated as a crude sample (column chromatography on sephadex LH20 ; after washing with H_2O, the adduct was eluted with MeOH/H_2O 1/1). Compounds 3 were separated after reduction with 40 mol equiv. of ascorbic acid then followed by column chromatography on Sephadex LH20 and elution as above. The nucleoside adducts 3a,b,c were obtained respectively in 50, 60 and 75 % yield based on the initial 9-OH-NME 1.

^{1}H NMR and Mass Data. ^{1}H NMR in CD_3COOD, coupling constants in Hz ; 3a : δ_H 2.76 (s, 5-Me), 3.40 (s, 11-Me), 3.77 (s, 3'-OMe), 3.93 (bs, $H'_5H''_5$), 4.40 (bs, H'_4), 4.54 (s, 2-Me), 4.57 (d, J4.2, H'_3), 6.02 (m, $H'_1H'_2$), 7.03 (s, H_2-adenine), 7.30 (bs, H_7H_8), 7.65 (s, H_8-adenine), 8.27 (d, J7, H_3 or H_4), 8.31 (d, J7, H_3 or H_4), 9.62 (s, H_1) ; 3b : δ_H 2.77 (m, H'_3, H''_3), 2.80 (s, 5-Me), 3.53 (s, 11-Me), 3.74 (d, J12, H'_5 or H''_5), 3.93 (d, J12, H'_5 or H''_5), 4.54 (s, 2-Me), 4.68 (m, H'_4), 5.79 (m,



H'_2), 6.16 (d, J4.8, H'_1), 7.20 (d, J8.6, H_7 or H_8), 7.26 (d, J8.6, H_7 or H_8), 7.59 (s, H_2-adenine), 7.8 (s, H_8-adenine), 8.31 (bs, H_3H_4), 9.78 (s, H_1) ; 3c : δ_H 2.78 (s, 5-Me), 3.52 (s, 11-Me), 4.04 (m, $H'_5H''_5$), 4.51 (s, 2-Me), 4.63 (m, H'_4), 4.96 (t, J4.0 and 4.0, H'_3), 5.54 (t, J4.0 and 3.8, H'_2), 6.32 (d, J3.8, H'_1), 7.20 (bs, H_7H_8), 7.91 (s, H_2-adenine), 8.13 (s, H_8-adenine), 8.24 (d, J7.2, H_3 or H_4), 8.29 (d, J7.2, H_3 or H_4), 9.73 (s, H_1) ; 4b, selected data : δ_H 6.21 (d, J9.8, H_7 or H_8), 7.66 (d, J9.8, H_7 or H_8). Mass-DCI (NH_3) : M peak at 556 (3a), M-adenine at m/z 421 (3a), 391 (3b), 407 (3c). .

RESULTS AND DISCUSSION

For the three compounds studied, arylation by elliptinium oxidized form occurs selectively on 2'-oxygen atom ; no others adducts could be detected. Final reduced structures 3a,b,c, are established from ^1H NMR and Mass data.

Possibility of formation of such adducts confirms that 2'-α-OH group could be the first step for the nucleoside arylation by the elliptinium acetate. These adducts might also represent models for further studies on arylation of ribonucleic acids where riboses (except for 3'-OH terminal ribose) have 3'-OH blocked by phosphate group and so allow a better understanding at a molecular level of the covalent binding of various RNA by elliptinium acetate (5).

ACKNOWLEDGMENTS

We are indebted to Pr. Imbach and Dr Gosselin for a gift of xylofuranosyl adenine, and to the SANOFI company for a gift of elliptinium acetate and financial support.

REFERENCES AND NOTES

1) In order to facilitate the discussion, α reffers to an hydroxy group below the ring sugar plane and β for an hydroxy above that plane.

2) B. Monsarrat, M. Maftouh, G. Meunier, B. Dugué, J. Bernadou, J.P. Armand, C. Picard-Fraire, B. Meunier and C. Paoletti. Biochem. Pharmacol. 1983, 34, 3887.

3) J. Bernadou, B. Meunier, G. Meunier, C. Auclair and C. Paoletti. Proc. Nat. Acad. Sci USA, 1984, 81, 1297.

4) V.K. Kansal, S. Funakoshi, P. Mangeney, P. Potier, B. Gillet, E. Guittet and J. Y. Lallemand.
Tetrahedron letters, 1984, 25, 2351.
5) B. Dugué, B. Meunier and C. Paoletti,
Biochem. Biophys. Res. Commun., in press.