

This article was downloaded by:

On: 26 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

Evidence for Cyclophosphate Formation During Hydrolysis of 3-Methyl-cycloSal-PCVMP

Andreas Lomp^a; Chris Meier^a; Markus Herderich^b; Peter Wutzler^c

^a Institut für Organische Chemie, Universität Hamburg, Hamburg, Germany ^b Institut für Lebensmittelchemie, Universität Würzburg, Würzburg, Germany ^c Institut für Antivirale Chemotherapie, Klinikum der Friedrich-Schiller-Universität Jena, Erfurt, Germany

To cite this Article Lomp, Andreas , Meier, Chris , Herderich, Markus and Wutzler, Peter(1999) 'Evidence for Cyclophosphate Formation During Hydrolysis of 3-Methyl-cycloSal-PCVMP', *Nucleosides, Nucleotides and Nucleic Acids*, 18: 4, 943 – 944

To link to this Article: DOI: 10.1080/15257779908041606

URL: <http://dx.doi.org/10.1080/15257779908041606>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

EVIDENCE FOR CYCLOPHOSPHATE FORMATION DURING HYDROLYSIS OF 3-METHYL-CYCLOSal-PCVMP

Andreas Lomp^a, Chris Meier^{a*}, Markus Herderich^b and Peter Wutzler^c

a) Institut für Organische Chemie, Universität Hamburg, Martin-Luther-King-Platz 6,
D-20146 Hamburg, Germany

b) Institut für Lebensmittelchemie, Universität Würzburg, Am Hubland
D-97074 Würzburg, Germany

c) Institut für Antivirale Chemotherapie, Klinikum der Friedrich-Schiller-Universität Jena,
Nordhäuser Str. 78, D-99089 Erfurt, Germany

Abstract: A hydrolysis study of 3-methyl-*cyclo*Sal-PCVMP **2** is described. Surprisingly, phosphotriester **5** released in this study not the expected PCVMP, but *cyclo*PCVMP.

Here we describe the properties of 3-methyl-*cyclo*saligenyl penciclovirmono-phosphate **2**. Penciclovir **1** and the title compound **2** were prepared according to syntheses that have been described previously^{1,2}.

Compound **2** has been studied for its lipophilic property (partition coefficient in *n*-octanol/water ($\log P$ value)) as well as for its hydrolytic stability in 25 mM isotonic PBS, pH 7.3. For this hydrolysis experiment we proceeded as described before³. The $\log P$ value, the half-life ($t_{1/2}$) and the rate constant k have already been published².

Surprisingly, 3-methyl-*cyclo*Sal-PCVMP **2** showed a pronounced decrease in half-life as compared to other *cyclo*Sal-NMP triesters². We assumed that the reason for this marked increase in hydrolytic lability could be either an assisting effect of the second, unprotected primary hydroxy group in the vicinity of the phosphate triester moiety due to a preorientation or an activation of the nucleophile water or a direct nucleophilic attack of this hydroxyl group at the phosphorus center. The consequences are i) the formation of PCVMP in the former case (except the rate acceleration) and ii) the formation of cyclic PCVMP **3** (*c*PCVMP). In order to identify the hydrolysis product of the chemical hydrolysis of 3-methyl-*cyclo*Sal-PCVMP **2** two experiments were conducted: First, a ³¹P-NMR experiment in a DMSO-*d*₆/water mixture containing small amounts of TRIS-buffer,

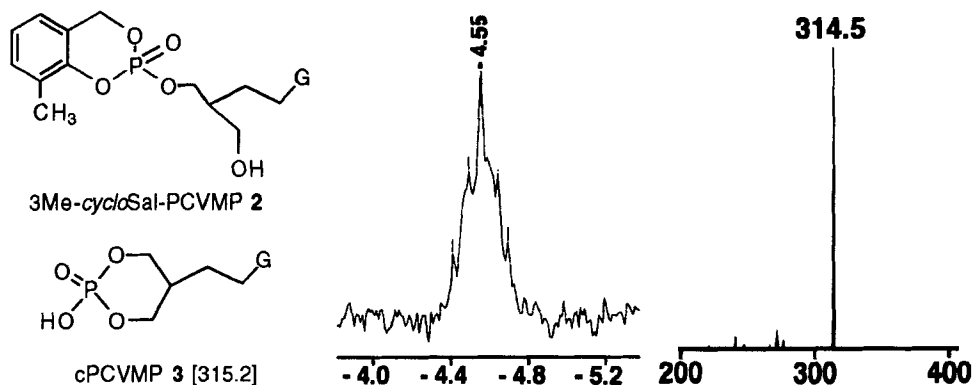


Figure 1: Structures of **2** and **3**, H-coupled ^{31}P -NMR and ESI-mass spectrum of hydrolysis product **3**

pH 8.8 was carried out. After complete hydrolysis, a proton-coupled ^{31}P -NMR spectrum was recorded. From the chemical shift and the coupling pattern of the phosphorus signal (a singlet at -4.5 ppm in the decoupled mode) it became apparent that the hydrolysis of **2** obviously did not lead to the expected PCVMP but to a product which showed a quintet in the proton-coupled mode (Figure 1). In contrast, PCVMP should split into a triplet in the proton-coupled mode of the ^{31}P -NMR spectrum⁴. Consequently, the multiplet observed strongly indicates the formation of the cPCVMP **3** (Figure 1). A further indication for the formation of cPCVMP **3** was taken from electrospray mass spectrometry. PCVMP has a mass of 333.2 u and should yield molecular ions $[\text{M}-\text{H}]^-$ and $[\text{M}-2\text{H}]^-$ at m/z 332 and m/z 165.5, respectively. However, the product observed in the NMR experiment was characterized by a molecular ion $[\text{M}-\text{H}]^-$ at m/z 314 (Figure 1). Further product ion experiments unambiguously demonstrated the presence of a phosphate moiety (m/z 97 and m/z 79). Hence, both experiments prove the formation of cPCVMP **3** (MW 315.2 g/mol) from the cycloSal-PCVMP derivatives **2** instead of PCVMP.

Compound **2** has been evaluated for its inhibition of HSV-1, HSV-1/TK⁻ and EBV replication in Vero and P3HR-1 cells. As expected, **2** devoid of any antiviral activity².

REFERENCES

1. Harnden, M.R.; Jarvest, R.L.; Bacon, T.H.; Boyd, M.R.; *J. Med. Chem.* **1987**, *30*, 1636-1642.
2. Meier, C.; Habel, L.; Haller-Meier, F.; Lomp, A.; Herderich, M.; Klöcking, R.; Meerbach, A.; Wutzler, P.; *Antiviral Chem. & Chemother.*, in press, **1998**.
3. Meier, C.; Lorey, M.; De Clercq, E.; Balzarini, J.; *J. Med. Chem.* **1998**, *41*, 1417-1427.
4. Meier, C.; Lorey, M.; De Clercq, E.; Balzarini, J.; *Bioorg. Med. Chem. Letters* **1997**, *7*, 99-104. Meier, C.; De Clercq, E.; Balzarini, J.; *Eur. J. Org. Chem.* **1998**, 837-846.