Tetrahedron Letters,Vol.26,No.47,pp 5785-5786,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF 3-DEAZAOXANOSINES, C-NUCLEOSIDE ISOSTERES OF OXANOSINE

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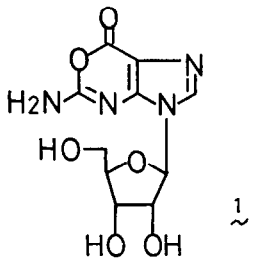
Abstract: The synthesis of 3-deazaoxanosines, C-nucleoside isosteres of oxanosine, is described.

During studying the cytotoxic effects of oxanosine 1[1,2] *in vivo*, we found that 1 degradated gradually in mammarian sera to yield the bioinactive product. The degradation was found to be due to an enzymatic hydrolysis of the oxazinone ring.[3] Therefore, we synthesized 1-methyl-3-deazaoxanosine 2 and 3-deazaoxanosine 3.



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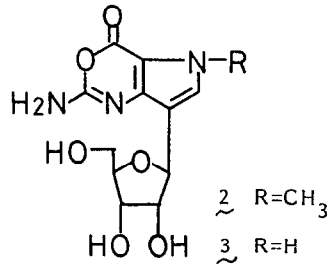
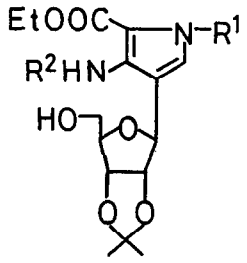


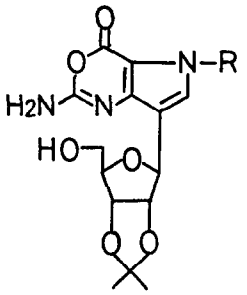
2 R=CH_3
3 R=H

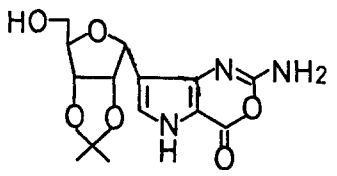
Attempts to form the oxazine ring from 4a[4,5] via S-methylisothiourea 5 in the similar manner to the oxazine ring formation in the synthesis of 1[6] were unsuccessful because of the formation of undesirable deazapurine analogues.

Direct cyanation of amino function of 4, however, gave good results. Treatment of amino-esters 4a and 4b[8] with BrCN (2 eq) in the presence of NaOAc (5 eq) in MeOH (rt, 20-24 hr) afforded ester-cyanamides 6a and 6b in 29% and 39% yield, respectively.[7]

Ring closure of the ester-cyanamides to oxazine ring was carried out under strongly basic conditions. Alkaline hydrolysis of 6a with 5N-methanolic KOH (reflux 30 min) followed by neutralization with 1N-HCl furnished the desired pyrrolo[3,2-d][1,3]oxazine 7a in 71% yield.[7] In the case of 6b, however, epimerization at C-1' occurred during alkaline hydrolysis. Treatment of 6b with 5N-KOHaq-EtOH (1:1)(reflux 15 min) followed by usual working up provided a mixture of 7b and its α-isomer 8 in a ratio of 2:3 in 72% yield.[9,10] The cyclization of α-isomer of 6b under the same conditions also gave the epimerized products [87%, ratio of 7b/8 (2:3)].[9,10] Finally, the removal of the protecting groups of 7a and 7b with 90% CF_3COOH (rt,







4a: $R^1=CH_3$, $R^2=H$ 4b: $R^1=H$, $R^2=H$

5: $R^1=CH_3$, $R^2=C(SCH_3)=N-COOC_2H_5$

6a: $R^1=CH_3$, $R^2=CN$ 6b: $R^1=H$, $R^2=CN$

7a: $R=CH_3$

7b: $R=H$

8

10 min) afforded 1-methyl-3-deazaoxanosine 2 and 3-deazaoxanosine 3 in 76% yield in both reactions.

Compounds 2 and 3 were resistant to the hydrolytic enzyme of mouse serum. But, they had much less bioactivity than oxanosine.

REFERENCES AND NOTES

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3. Unpublished results
4. N-methyl derivative (4a) was synthesized in a similar manner to the preparation of N-benzyl derivative.[5]
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7. All samples were characterized by infrared, nuclear magnetic resonance (400 MHz) and mass spectral data.
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9. The configuration at C-1' in 7a, 7b and 8 were assigned from the chemical shifts in their H^1-NMR spectra.

Chemical shifts for H-1'

Compd.	7a*	7b+	8+
ppm	4.79	4.82-4.87++	5.23

*: $CDCl_3$, +: CD_3COCD_3, ++: overlapped with H-2' signal

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(Received in Japan 18 September 1985)