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REACTION OF ADENINE WITH AN α-CHLOROOXETANE: AN APPROACH TO THE SYNTHESIS OF OXETANE NUCLEOSIDES

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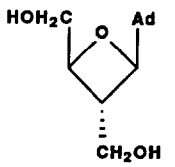
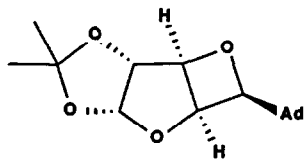
The reaction of adenine with 3,5-anhydro-5R-chloro-1,2-O-isopropylidenexylofuranose, a stable α-chlorooxetane, gives a mixture of the two epimers of 5-[9-adenyl]-3,5-anhydro-1,2-O-isopropylidenexylofuranose; the structure of 5R-[9-adenyl]-3,5-anhydro-1,2-O-isopropylidenexylofuranose was established by X-ray crystallography.

Oxetanocin (1), a novel oxetane-containing nucleoside,[1,2] possesses antiviral, antitumour and antibacterial properties and has been shown to inhibit HIV infectivity.[3] A synthesis of oxetanocin has recently been reported[4] from a β-ribopyranosyladenine derivative.[5] An alternative strategy for the synthesis of oxetane nucleosides might involve nucleophilic substitution of an α-halooxetane by a suitable heterocyclic base; this paper describes the conversion of the α-chlorooxetane (4) to the epimeric oxetane nucleoside analogues (2) and (3). The structure of 5R-[9-adenyl]-3,5-anhydro-1,2-O-isopropylidenexylofuranose (2) was confirmed by X-ray crystallography.



(1)



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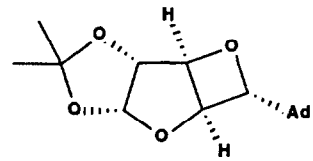

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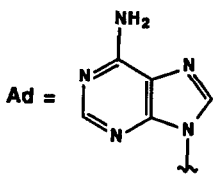

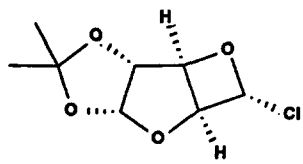

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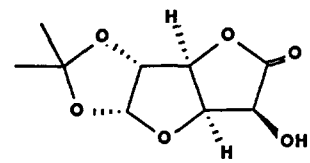
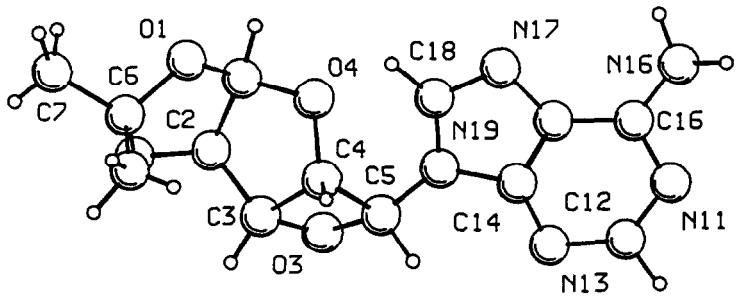


(5)

3,5-Anhydro-5R-chloro-1,2-O-isopropylidenexylofuranose (4), readily prepared from the protected glucuronolactone (5),[6] was stirred with adenine and anhydrous potassium carbonate in acetonitrile:dimethyl formamide (1:1) in the presence of 18-crown-6 at 100°C. The crude product was purified by flash chromatography to give a mixture of the two epimeric adenine oxetane nucleoside analogues (2) and (3) in approximately a 1:1 ratio in 50% yield. Careful flash

chromatography and crystallisation gave pure samples of the more polar 5R-[9-adenyl]-3,5-anhydro-1,2-O-isopropylidenexylofuranose (2), m.p. 230°-233°C (from methanol), $[\alpha]_D^{20}$ +80° (c, 0.06 in MeOH) and of the less polar 5S epimer (3), m.p. 154°-156°C (from acetone), $[\alpha]_D^{20}$ +61° (c, 0.16 in MeOH). The formation of both epimers in this reaction may indicate that the nucleophilic displacement has significant S_N1 character.



Crystal structure of 5R-[9-adenyl]-3,5-anhydro-1,2-O-isopropylidenexylofuranose(2)

The structures of (2) and (3) were consistent with spectroscopic and microanalytical data obtained and the structure of (2) was confirmed by X-ray crystallography. The crystal structure of (2) shows that, in contrast to the case of the chloro compound (4) where the oxetane ring is planar, the four membered ring is somewhat buckled (deviations up to 0.09 A from the mean plane) and the adenine moiety occupies the endo site of C-5.[7]

Although the yield for the coupling reaction between the halo oxetane and the heterocyclic base has not yet been optimised, these preliminary results indicate that this approach may provide a viable strategy for the synthesis of oxetane nucleosides; the scope and limitations of the use of α-halooxetanes in this reaction are currently being investigated.[8]

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7. The details of the crystal structure of (2) will be given in a full paper.
8. We acknowledge SERC postdoctoral fellowships (to JCS and KV). TAH was on leave from Department of Chemistry, University of Birmingham, UK. We are grateful to Drs. Myers, Newton and Wallis of Glaxo Group Research for help in this project.

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