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Synthesis of Bicyclic Pyrimidine Nucleoside Derivatives

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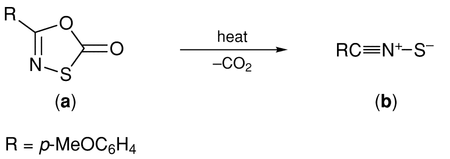
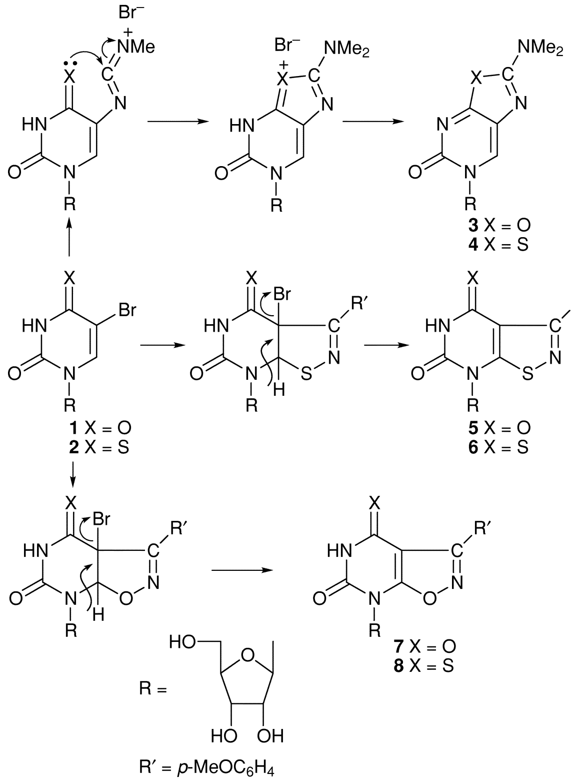
The reaction of 5-bromouridine and its 4-thio derivative with both nitrile sulfides and oxides is described.

It is known[13–15] that 5-(*p*-methoxyphenyl)-1,3,4-oxathiazol-2-ones (**a**) are thermally labile and fragment on vigorous heating to regenerate the 5-(*p*-methoxyphenyl)nitrile sulfide (**b**) in a retro-1,3 dipolar cycloaddition reaction. Reactions of 5-bromouridine and its 4-thio analogue with both nitrile sulfides and oxides have been described. It is important to mention that *p*-nitrobenzohydroximoyl chloride (**c**) was employed as *p*-benzonitrile oxide (**d**).



$$p\text{-}O_2NC_6H_4CCl{=}NOH \xrightarrow[-HCl]{heat} p\text{-}O_2NC_6H_4 \quad C{\equiv}N^+{-}O^-$$

(**c**) (**d**)



Scheme 1

Both 5-bromouridine and its 4-thio analogue were prepared by the reaction of uridine or 4-thiouridine with bromine water. Consequently, the reaction of 5-bromouridine or its 4-thio analogue with dimethylcyanamide is presumably at first *via* its ammonium chloride salt, then nucleophilic addition of the oxygen atom at C-4 of the uracil ring to the cyanamide carbon atom gives the 4,5-cyclised products with positively charged ring oxygen atoms. This effect may be favoured by the near coplanarity of the nitrogen atoms. Loss of hydrogen bromide gives compounds **3** and **4**, which in the ^{1}H-NMR spectra (CDCl$_3$) display a singlet (δ 3.4) which is characteristic for the dimethylamino group. Therefore oxathiazoles might act as nitrile sulfide precursors.

On thermolysis, 1,3,4-oxathiazoles undergo 1,3-dipolar cycloaddition forming nitrile sulfides. Electron donating substituents increase the oxathiazole fragmentation rates. Reactions of both 5-bromouridine and its 4-thio analogue with *p*-methoxybenzonitrile sulfide and *p*-methoxybenzonitrile oxide provides 5,6-cyclised products, presumably *via* nucleophilic attack of either the nitrile sulfide or nitrile at C-6 the nucleophilic attack at C-5 of the uracil ring to the nitrile carbon atom α to nitrogen. Abstraction of the acidic H-6 and expulsion of bromide gave compounds **5**–**8** respectively. The IR spectra showed characteristic C=N absorption at 1650 cm^{-1}. The products were identified from their analytical and spectroscopic data.

Techniques used: ^{1}H NMR, IR, MS

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