An Easy Access to 5-Mercaptopyrimidine Nucleosides through One-step Synthesis of 5-Thiocyanato-uridine and -2′-deoxyuridine

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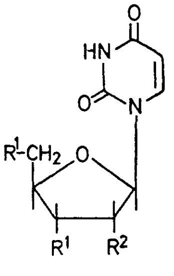
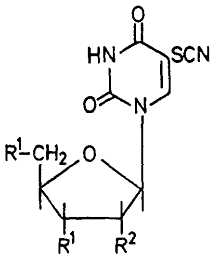
Summary Reaction of uridine or 2′-deoxyuridine with thiocyanogen chloride gives the 5-thiocyanato-derivatives in good yield; this novel electrophilic substitution reaction of pyrimidine nucleosides opens a direct approach to the biologically active 5-mercaptopyrimidine nucleosides.

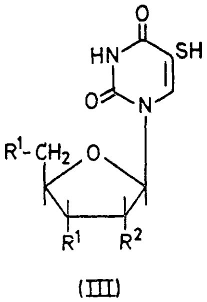
5-Mercaptouridine (IIIa)[1] and 5-mercapto-2′-deoxyuridine (IIIb)[2] possess significant antibacterial and antitumour activities. Previous methods [1,3] for the preparation of these nucleosides made use of a modified Hilbert–Johnson procedure, *i.e.*, coupling of a carbohydrate moiety with the mercaptopyrimidine. We report a direct synthesis of 5-thiocyanatouridine (IIa) and 5-thiocyanato-2′-deoxyuridine (IIb) by thiocyanation of the pyrimidine nucleosides (Ia,b) with thiocyanogen chloride.[4] The thiocyanato-derivatives are then readily reduced to the corresponding mercapto-analogues.



(I)



(II)



(III)

a; $R^1 = R^2 = OH$
b; $R^1 = OH$, $R^2 = H$
c; $R^1 = R^2 = OAc$

To a cooled solution of dry chlorine gas (50 mmole) in glacial acetic acid was added dry potassium thiocyanate (55 mmole), and the mixture was stirred for 20 min at room temperature. Uridine (5 mmole) was then added and and the mixture was stirred for 1 h with exclusion of moisture. Cyclohexene was added to destroy the excess of thiocyanogen chloride. 5-Thiocyanatouridine (IIa)† was obtained in 48% yield, m.p. 167—172° (from ethanol) [λ_{max} (MeOH) 273 nm (ϵ 10,400); ν_{max} (Nujol) 2160 cm^{-1} (-SCN); τ (CD$_3$OD) 1·12 (N–C*H*=CSCN)]. When the reaction was carried out with the protected nucleoside, 2′,3′,5′-triacetyluridine (Ic), the 5-thiocyanato-derivative (IIc) was obtained in 96% yield as an amorphous solid (10 h reaction period). In a similar manner 2′-deoxyuridine (Ib) gave 5-thiocyanato-2′-deoxyuridine (IIb) in 55% yield, m.p. 183—184·5° (from ethanol). The spectral characteristics of both (IIb) and (IIc) resembled those of (IIa).

5-Thiocyanatouridine (IIa) was reduced to 5-mercaptouridine (IIIa)‡ by 10^{-3} M-dithiothreitol[5] in 0·1 M-EDTA buffer (pH 7·8) (2 min reaction period) or by sodium dithionite–mercaptoethanol[6] (15 min reaction period).

While the thiocyanation of properly substituted olefins,[7] aromatic compounds,[8] and pyrrole carboxylates[9] has been described, the addition to $\alpha\beta$-unsaturated olefins containing electron-withdrawing substituents does not normally occur.[10] The addition of thiocyanogen chloride to uridine follows the Markownikov rule, in analogy to other pseudohalogens, such as trifluoromethyl hypofluorite.[11,12]

The 5-thiocyanatopyrimidine nucleosides (IIa—c) are at present being screened for biological and antineoplastic activities. These compounds are of interest, since they may also exert biological activity after *in vivo* reduction to the corresponding mercaptans, or they may behave like 5-halogenopyrimidine nucleosides,[13] due to the pseudohalogen nature of the thiocyanato-group.

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† Correct elemental analyses were obtained for all 5-thiocyanato-nucleosides.

‡ Identical with an authentic sample (u.v. spectra and t.l.c. R_F values in two solvent systems) kindly provided by Dr. T. J. Bardos.

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