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SYTHESIS OF 5-ETHYNYLCYTOSINE AND 5-ETHYNYLCYTIDINE

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There has been great interest in 5-substituted pyrimidine nucleosides as antiviral and anticancer agents.[1,2] Recently we have reported the synthesis of 5-ethynyluracil[3] and Bobek and coworkers have reported the synthesis of the same compound and 5-ethynyl-2'-deoxyuridine[4] and have shown that the latter has significant antiviral and anticancer activities.[5,6] We have recently shown that 5-ethynyluracil inhibits the growth of Mycoplasma mycoides subsp. capri to the extent of 50% at 41μg/ml and of Escherichia coli 15T⁻ at 0·5μg/ml.[7] Being as some 5-substituted 2'-deoxycytidine derivatives also show antiviral activity[8] it is obviously of particular interest to synthesise 5-ethynylcytosine and its nucleosides. The synthesis of some of these compounds is outlined in this paper.

5-(1-Chlorovinyl)-2,4-dichloropyrimidine (1a)[3] was treated with ethanolic ammonia at 0°C for 18h to give a mixture of 2-amino-4-chloro-5-(1-chlorovinyl)pyrimidine (1b) and 4-amino-2-chloro-5-(1-chlorovinyl)pyrimidine (1c). Part of the latter was obtained pure by crystallisation from ethanol and the remainder by column chromatography on silica gel (yield 28%), m.p. 178-179°(d). N.m.r. (DMSO d6/D_2O) δ, 5·85 (2H, m, vinylic H), 8·18 ppm (1H, s, H-6). It was homogeneous by t.l.c. in six solvent systems. Compound 1b was obtained pure after separation on the silica column and subsequent crystallisation from chloroform (yield 11%), m.p. 159-160°(d). N.m.r. (DMSO d6/D_2O) δ, 5·85 (2H, m, vinylic H), 8·38 ppm (1H, s, H-6). The chemical shift corresponding to the H6 proton in 1b and 1c (8·38 and 8·18 ppm respectively) was consistent with that quoted elsewhere in the case of similar compounds.[9] 1c was converted in 70% yield to 5-ethynylcytosine (2a) upon treatment with 2M potassium hydroxide in boiling dioxan-water (1:1) for 1·5h. The structure of 2a was established by comparison of its u.v. spectrum with that of 5-ethylcytosine;[10] its n.m.r. spectrum, and the fact that 2a could also be obtained by the action of ammonia on 4-ethoxy-5-ethynyl-2-(1H)-pyrimidone (2b), a compound whose structure has already been established.[3] 5-Ethynylcytosine showed the following characteristics: m.p.>225°, λ_{max} 238nm, 301nm, λ_{min} 263nm at pH 1; λ_{max} 235nm, 288nm, λ_{min} 265nm at pH 7; λ_{max} 256nm, 303nm, λ_{min} 277nm at pH 12. N.m.r. (DMSO d6/D_2O) δ, 4·35 (1H, s, ethynyl H), 7·88 ppm (1H, s, H-6).

In order to prepare the ribonucleoside, 2c was converted into its trimethylsilyl derivative by treatment with hexamethyldisilazane and trimethylsilyl chloride followed by purification by distillation in vacuo (yield 90%). This trimethylsilyl derivative was reacted with 1-O-acetyl-2,3,5-tri-O-benzoylribofuranose in dichloroethane in the presence of stannic chloride as catalyst to give 2',3',5'-tri-O-benzoyl-5-ethynylcytidine (2d) (90% yield of crude product) which

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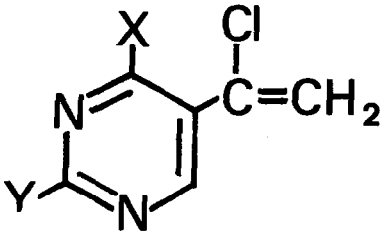
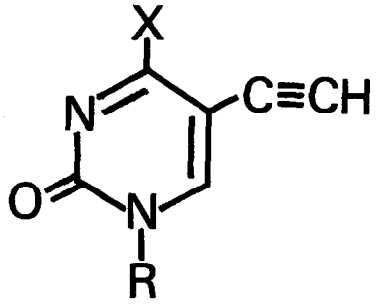


1

1a, X = Y = Cl
1b, X = Cl; Y = $-NH_2$
1c, X = $-NH_2$; Y = Cl



2

2a, X = $-NH_2$; R = H
2b, X = $-OEt$; R = H
2c, X = $-NH_2$; R = β-D-ribofuranosyl-
2d, X = $-NH_2$; R = 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl-

was crystallised from ethanol to give the pure product, m.p. 203-205°(d). N.m.r. ($CDCl_3$) δ, 2·95 (1H, s, ethynyl H), 6·16 ppm (1H, d, J = 7Hz, H-1'). This n.m.r. spectrum showed that the compound is a β nucleoside. The benzoyl groups were removed by treatment with sodium methoxide to give 5-ethynylcytidine (2c) in 94% yield. The compound decomposed on heating at about 160°. λ_{max} 236, 302nm, λ_{min} 261nm at pH 1; λ_{max} 235, 292nm, λ_{min} 264nm at pH 7; λ_{max} 227, 296nm, λ_{min} 267nm at pH 12. N.m.r. (DMSO d6/D_2O) δ, 4·30 (1H, s, ethynyl H), 5·76 (1H, d, H1'), 8·36 ppm (1H, s, H-6).

All the compounds gave acceptable elemental analysis for carbon, hydrogen, and nitrogen and for chlorine where appropriate. Compounds 2a and 2c are being tested for biological activity.

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