Some Chemical Reactions of 5-Vinyluracil and 2′-Deoxy-5-vinyluridine

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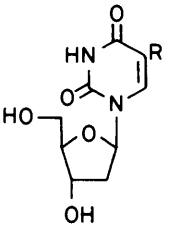
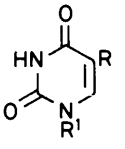
In an attempt to elucidate the chemical reactions responsible for the antiviral and toxic properties of 2′-deoxy-5-vinyluridine (**1**), the chemistry of some 5-vinyluracil derivatives has been studied. Under aqueous acidic conditions 5-vinyluracil (**5**) is in equilibrium with 5-(1-hydroxyethyl)uracil (**6**) and the dimer, (*E*)-1,3-bis(uracil-5-yl)but-1-ene (**9**). The formation of (**9**) is favoured in concentrated solution. Upon treatment with aqueous acid compound (**1**) gives 2′-deoxy-5-(1-hydroxyethyl)uridine (**4**) but no dimerisation occurs. 1-Ethyl-5-vinyluracil (**7**) has been synthesized and this in hydrochloric acid gives the dimer, (*E*)-1,3-bis(1-ethyluracil-5-yl)but-1-ene (**10**). Under similar conditions compound (**5**) reacts with L-cysteine to give 5-(1-L-cystein-*S*-ylethyl)uracil (**11**) and with phenol to give a mixture of substituted phenols. Compound (**1**) reacts with butan-1-ol in the presence of trifluoroacetic acid to give 5-(1-butoxyethyl)-2′-deoxyuridine (**14**); under more vigorous conditions 5-(1-butoxyethyl)uracil (**13**) was formed. In 1M hydrochloric acid at 100 °C compound (**1**) reacts with phenol to give a mixture of substituted phenols. From this mixture 2′-deoxy-5-[1-(4-hydroxyphenyl)ethyl]uridine (**17**) was isolated and characterised. In a similar manner compound (**1**) reacted with 4-propan-2-ylphenol to give 2′-deoxy-5-[1-(2-hydroxy-5-propan-2-ylphenyl)ethyl]uridine (**18**). Treatment of compound (**1**) with *m*-chloroperbenzoic acid in water–tetrahydrofuran gave 2′-deoxy-5-(1,2-dihydroxyethyl)uridine (**19**) which was characterised as its tetra-*O*-acetate (**20**).

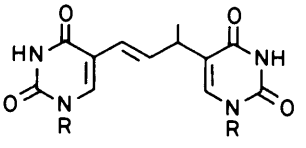
2′-Deoxy-5-vinyluridine (**1**) is a nucleoside analogue which shows a wide range of biological activities. It is active against a number of viruses including HSV-1 and HSV-2[1,2] and in tissue culture it inhibits the growth of L1210 leukaemia cells.[3] It also causes damage to chromosomes at low concentration.[4] If supplied in the form of the free base, 5-vinyluracil (**5**) it is incorporated into the DNA of some micro-organisms[5–8] and in one case, namely in *Mycoplasma mycoides* var. *capri*, its presence sensitised the cells to γ radiation.[7] With regard to its antiviral activity and its incorporation into DNA, (**1**) resembles 2′-deoxy-5-ethyluridine (**2**)[1,9–11] but differs from (**2**) with regard to its effect on chromosomes [(**2**) is not mutagenic[11]]. In this respect compound (**1**) more closely resembles 2′-deoxy-5-hydroxymethyluridine (**3**) which is cytostatic, a property which has been attributed to the ability of the 5-hydroxymethyl group to form crosslinks between DNA and proteins.[12] It appears that much of the biological activity of (**1**) could be due to the chemical reactivity of the 5-vinyl group of the residues of (**1**) incorporated into the DNA of the organism. In the present work a study of the chemical reactions of (**1**) and of its free base (**5**) has been made with emphasis on those reactions which might be responsible for biological activity.



(**1**) R = —CH=CH$_2$
(**2**) R = Et
(**3**) R = —CH$_2$OH
(**4**) R = —CH(OH)Me



(**5**) R = —CH=CH$_2$, R^1 = H
(**6**) R = —CH(OH)Me, R^1 = H
(**7**) R = —CH(OH)Me, R^1 = Et
(**8**) R = Ac, R^1 = Et



(**9**) R = H
(**10**) R = Et

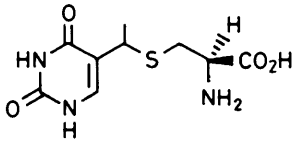
In our early work on the synthesis of 5-vinyluracil (**5**) by dehydration of 5-(1-hydroxyethyl)uracil (**6**) under acidic conditions it was shown that a major product was the dimer of (**5**) (*E*)-1,3-bis(uracil-5-yl)but-1-ene (**9**).[13] In the present work these experiments were repeated and it was shown that in aqueous acidic solution an equilibrium exists between (**5**), (**6**), and (**9**) which favours (**9**) in concentrated solution where the compound is precipitated. The possibility that (**1**) might undergo similar reactions was then investigated. It was found that no dimer analogous to (**9**) was formed. The major product was 2′-deoxy-5-(1-hydroxyethyl)uridine (**4**). The latter compound was isolated and characterised; it appears that this was one of the two possible diastereoisomers. Under the strongly acidic conditions used, a small amount of hydrolysis of the glycosidic linkage occurred.

In order to establish that this lack of dimerisation was not due to the presence of a substituent at N-1, 1-ethyl-5-(1-hydroxyethyl)uracil (**7**) was synthesized by the reduction of 5-acetyl-1-ethyluracil (**8**). The latter was obtained from diketene by an analogous route to that used to synthesize 5-acetyluracil.[14] Treatment of (**7**) with 2M hydrochloric acid at 75 °C gave a precipitate which was isolated and characterised as the expected dimer, (*E*)-1,3-bis(1-ethyluracil-5-yl)but-1-ene (**10**) (13%). The lack of dimerisation in the case of (**1**) could be due to steric hindrance, but it appears more probable that it is due to solubility; (**9**) and (**10**) are relatively insoluble in aqueous acid so that their formation is favoured whereas a dimer of (**1**) might be more soluble so that its formation would not be so favoured.

Although no dimerisation of (**1**) could be obtained, this does not exclude the possibility that cross-linking of DNA containing 5-vinyluracil residues might be responsible for the biological

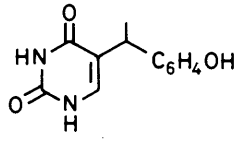
activity of (**1**). On the other hand the results do not support such a hypothesis.

Another possibility is that the biological activity of (**1**) could be due to the reaction of 5-vinyluracil residues in DNA with nucleophilic groups in proteins as has been postulated to account for the cytostatic activity of (**3**)[12] by a mechanism in which under effectively acidic conditions the CH_2OH group would form a carbonium ion which would then react with nucleophilic groups in proteins. Under acidic conditions the 5-vinyl group would also form a carbonium ion. The most likely groups to react in proteins are thiol and hydroxy. It has already been shown by Lipnick and Fissekis[15] that 5-(1-hydroxyethyl)-uracil (**6**) reacts with L-cysteine to give a mixture of diastereoisomers of structure (**11**).



(**11**)

We have shown that 5-vinyluracil (**5**), as expected, gives the same products. Reaction of (**5**) with alcohols, *e.g.* ethanol and L-serine, was complicated by the predominant formation of the dimer (**9**). Compound (**5**) did react with phenol in trifluoroacetic acid, but not with the hydroxy group; the product was a mixture of ring-substituted phenols of the general structure (**12**).

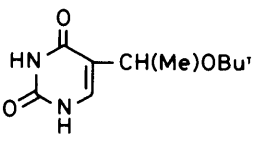


(**12**)

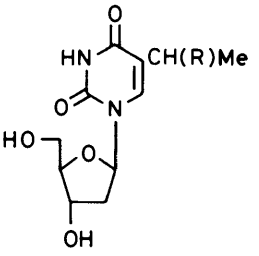
Since 2′-deoxy-5-vinyluridine (**1**) does not form a dimer under acidic conditions, it was expected that it would react with alcohols. This proved to be the case; reaction with butan-1-ol in the presence of trifluoroacetic acid at 55 °C gave 5-(1-butoxyethyl)-2′-deoxyuridine (**13**) as a mixture of diastereoisomers in 15% yield. When (**1**) was treated with butan-1-ol under more vigorous conditions (saturated HCl in dioxane at 75 °C) very little compound (**14**) was formed and the major product was 5-(1-butoxyethyl)uracil (**13**). Compound (**1**) was also treated with phenol in hydrochloric acid at 100 °C to give two components which ran close together on t.l.c. These were isolated; the faster running component had an n.m.r. spectrum which indicated that it was probably a mixture of the *ortho*- and *meta*-substituted phenols (**15**) and (**16**). The slower running component was shown to be the *para*-substituted phenol, (**17**) by elemental analysis, reaction with $FeCl_3$ and u.v., n.m.r., and mass spectra. In view of the fact that this reaction gave a mixture of products, compound (**1**) was treated with 4-propan-2-ylphenol in the presence of trifluoroacetic acid. This gave 5-[1-(2-hydroxy-5-propan-2-ylphenyl)ethyl]-2′-deoxyuridine (**18**) as a mixture of diastereoisomers in 45% yield.

Compound (**1**) reacts readily with thiols, *e.g.* thiophenol derivatives, to give either 5-(1-substituted)ethyl derivatives or 5-(2-substituted)ethyl derivatives depending upon whether a free radical inhibitor is present or not. These reactions have been reported in detail elsewhere.[16]

The results suggest that it is possible that some of the biological properties of compound (**1**) could be due to the reaction of the 5-vinyl group with the thiol, hydroxy, and phenyl groups of proteins. The conditions used here are, of course, highly acidic, but such conditions could be effectively present at the active sites of enzymes and at other domains of proteins.

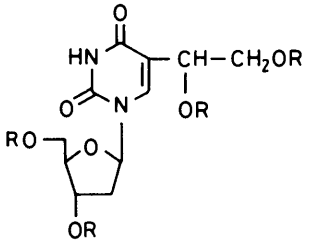


(**13**)



(**14**) R = OBu
(**15**) R = C_6H_4OH-*o*
(**16**) R = C_6H_4OH-*m*
(**17**) R = C_6H_4OH-*p*
(**18**) R = C_6H_3OH-2,Pr^i-4

Another reaction of the 5-vinyl group of compound (**1**) which could be relevant to biological activity is oxidation. A likely product of such an oxidation is an epoxide which could then react with nucleophiles. To simulate such an oxidation compound (**1**) was treated with *m*-chloroperbenzoic acid. The reaction was carried out in the absence of water, but the expected epoxide was not obtained. Instead the product appeared to be that which was produced by the opening of the epoxide ring by *m*-chlorobenzoate, although this product was not definitely characterised. When the oxidation was carried out in the presence of water the product was 2′-deoxy-5-(1,2-dihydroxyethyl)uridine (**19**) which was characterised as its tetra-*O*-acetate (**20**) [both (**19**) and (**20**) are mixtures of diastereoisomers]. It appears, therefore, that an epoxide is formed and that it is very reactive, the epoxide ring being easily opened by nucleophiles.



(**19**) R = H
(**20**) R = OAc

These studies have shown the very reactive nature of the 5-vinyl group of 2′-deoxy-5-vinyluridine and indicate possible mechanisms for the biological activities of this compound. They are only indications, however, and proof must await the identification of products formed by compound (**1**) in living cells.

Experimental

N.m.r. spectra were recorded on 100 MHz (Perkin-Elmer R14 and Varian XL100) and 250 MHz (Brucker) spectrometers with $(CD_3)_2SO$ as the solvent and u.v. spectra were measured on a Perkin-Elmer 552 spectrometer. Mass spectra were obtained on a Kratos MS 80 RF mass spectrometer using electron impact (e.i.), chemical ionisation (c.i.) using methane as reactant gas or fast atom bombardment (f.a.b.) using glycerol. Column chromatography was carried out on silica gel, Kieselgel 60 type 7734, 0.063—0.200 mm, 70—230 mesh ASTM (E. Merck A. G.,

Darmstadt, W. Germany). All evaporations of solvents were carried out under reduced pressure.

(E)-1,3-*Bis*(*uracil*-5-*yl*)*but*-1-*ene* (**9**).—(*a*) 5-(1-Hydroxyethyl)uracil (**6**) (700 mg, 4.5 mmol) was dissolved in formic acid (98%; 35 ml) and the solution heated to 105—110 °C for 30 min. The solution was evaporated to dryness and the residue extracted with boiling water (3 × 60 ml). The residue was dried to give the product (300 mg, 48% yield), m.p. 305 °C (decomp.) identical with the compound previously prepared:[13] $\lambda_{max.}$ 245 nm (ε 15 800) and λ_{sh} 271 nm (ε 11 800) in water, pH 1; δ 1.2 (3 H, d, CH_3), 3.3 (1 H, m, 3-H), 6.0 (1 H, d, vinylic 1-H, $J_{1,2}$ 14 Hz), 6.5 (1 H, dd, vinylic 2-H, $J_{1,2}$ 7 Hz), 7.1 (1 H, s, uracil 6-H), 7.5 (1 H, s, uracil 6-H), and 10.75—11.1. (4 H, 2 brs, NH); *m/z* (e.i.) 276 (M^+) and 261 ($M^+ - CH_3$).

(*b*) 5-Vinyluracil (**5**) (300 mg, 2.2 mmol) was heated in 1M hydrochloric acid (130 ml) at 80 °C for 30 min. The solution was then evaporated to dryness, 1M hydrochloric acid (130 ml) added, and the mixture again heated to 80 °C for 30 min. It was then evaporated to dryness and the resulting solid was extracted with boiling water and dried to give the product as a white solid (75 mg, 25%). It was identical with that prepared by method (*a*). When the reaction solution was examined immediately after the initial heating at 80 °C the major product was compound (**6**).

2′-*Deoxy*-5-*vinyluridine* (**1**).—This compound was synthesized by the method previously described.[16]

Action of Acid on 2′-*Deoxy*-5-*vinyluridine* (**1**).—Compound (**1**) was treated with formic acid and with hydrochloric acid under the conditions described above. Examination of the products by t.l.c. showed that the major product was 2′-deoxy-5-(1-hydroxyethyl)uridine (**4**) and that no dimer was present. Hydrolysis of the glycoside linkage occurred to a small extent to give mainly compound (**6**).

2′-*Deoxy*-5-(1-*hydroxyethyl*)*uridine* (**4**).—A solution of compound (**1**) (500 mg, 2.0 mmol), in 0.1M hydrochloric acid (80 ml) was kept at 90 °C for 4 h. After cooling, the solution was neutralised with an anion exchange resin [Zeolit FF(1P), OH^- form], the resin well washed with water and the filtrate and washings combined and evaporated to dryness. The solid residue was purified by column chromatography. The column was eluted with chloroform–methanol (4:1), appropriate fractions being collected and evaporated to dryness, and the residue crystallised from ethanol–toluene to give the *product* (200 mg, 37%) (Found: C, 48.2; H, 6.2; N, 10.0. $C_{11}H_{16}N_2O_6$ requires C, 48.5; H, 5.9; N, 10.3%); $\lambda_{max.}$ 266 nm (ε 9 740) in water, pH 1; $\lambda_{max.}$ 265 nm (ε 7 970) in water, pH 13; δ 1.24 (3 H, d, CH_3), 2.08 (2 H, m, 2′-H), 3.53 (2 H, m, 5′-H), 3.77 (1 H, m, 4′-H), 4.22 (1 H, m, 3′-H), 4.54 (1 H, q, C*H*(OH)CH_3), 4.92 (3 H, m, CH(O*H*)CH_3, 3′-OH, 5′-OH), 6.20 (1 H, t, 1′-H), and 7.71 (1 H, s, 6-H).

5-*Acetyl*-1-*ethyluracil* (**9**).—Ethylamine (10 ml) was added to a suspension of α-acetyl-β-ethoxy-*N*-ethoxyacrylamide (20 g, 87 mmol)[14] in water (100 ml) and the mixture warmed to effect complete dissolution. The clear solution was cooled and adjusted to pH 6 with glacial acetic acid. The resulting precipitate was filtered off and crystallised from ethanol to give the *product* as white prisms (11.8 g, 75% yield), m.p. 178 °C (Found: C, 53.0; H, 5.6; N, 15.7. $C_8H_{10}N_2O_3$ requires C, 52.75; H, 5.5; N, 15.4%); $\lambda_{max.}$ 232 nm (ε 9 100), 286 nm (ε 12 000), $\lambda_{min.}$ 251 nm (ε 1 380) in water, pH 1; $\lambda_{max.}$ 289 nm (ε 9 650) in water, pH 13; δ 1.20 (3 H, t, CH_2CH_3), 2.44 (3 H, s, $COCH_3$), 3.82 (2 H, q, CH_2CH_3), and 8.37. (1 H, s, 6-H); *m/z* (e.i.) 182 ($M^+ - CH_3$), and 139 ($M^+ - COCH_3$).

1-*Ethyl*-5-(1-*hydroxyethyl*)*uracil* (**7**).—Sodium borohydride (7.24 g, 0.19 mol) was added to a solution of compound (**8**) (9.0 g, 49.5 mmol) in 0.1M sodium hydroxide (650 ml) and the mixture was kept in the dark at *ca.* 20 °C for 18 h. The solution was then neutralised with an anion exchange resin (Dowex 50W × 8, H^+ form), the resin filtered off, washed well with water and the filtrate and washings combined and evaporated to dryness. The resulting oil was co-evaporated with methanol to remove borate, triturated with acetone, and purified by column chromatography using chloroform–methanol (4:1) as the eluant. Appropriate fractions were collected and evaporated to dryness to give the *product* as a white powder (8.7 g, 95% yield) (Found: C, 52.3; H, 6.9; N, 15.5 $C_8H_{12}N_2O_3$ requires C, 52.2; H, 6.6; N, 15.2%); $\lambda_{max.}$ 271 nm (ε 9 040) in water, pH 1; $\lambda_{max.}$ 269 nm (ε 6 500) in water, pH 13; δ 1.15 (3 H, t, CH_2CH_3), 1.30 [3 H, d, CH(OH)CH_3], 3.72 (2 H, q, CH_2CH_3), 4.55 [1 H, q, C*H*(OH)CH_3], 5.0 (1 H, brs, OH), 7.55 (1 H, s, 6-H), and 11.15 (1 H, brs, NH).

(E)-1,3-*Bis*(1-*ethyluracil*-5-*yl*)*but*-1-*ene* (**10**).—A solution of compound (**7**) (1.0 g, 5.4 mmol) in 2M hydrochloric acid (40 ml) was kept at 75 °C for 2 h. The resulting white precipitate was filtered off, washed with water, and dried to give the *product* (280 mg, 31% yield) (Found: C, 54.3; H, 6.3; N, 16.0. $C_{16}H_{20}N_4O_4 \cdot H_2O$ requires C, 54.8; H, 6.3; N, 16.0%); $\lambda_{max.}$ 243 nm (ε 25 000) and 275 nm (ε 22 300); $\lambda_{min.}$ 265 nm (ε 21 500) in water, pH 1; $\lambda_{max.}$ 228 nm (ε 15 580), 250 nm (ε 14 880), $\lambda_{min.}$ 246 nm (ε 14 860) in water, pH 13; δ 1.20 (9 H, m, CH_3CH, $2CH_3CH_2$), 3.70 (4 H, q, $2\text{-}CH_2CH_3$), 6.05 (1 H, d, vinylic 1-H, $J_{1,2}$ 16 Hz), 6.50 (1 H, dd, vinylic 2-H, $J_{1,2}$ = 16 Hz, $J_{2\text{-H,CH}}$ 8 Hz), 7.40 (1 H, s, 6-H), 7.77 (1 H, s, 6-H), and 11.17 (2 H, brs, NH) (Found: *m/z* (e.i.) 332.1457 $C_{16}H_{20}N_4O_4$ requires M^+; 332.1484).

5-(1-*Cystein*-S-*ylethyl*)*uracil* (**11**). A solution of 5-vinyluracil (600 mg, 4.3 mmol) and L-cysteine (484 mg, 4 mmol) in 1.5M hydrochloric acid was maintained at 70 °C for 70 h. After work-up in a similar manner to that described by Lipnick and Fissekis[15] a similar mixture of partly-separated diastereoisomers was obtained (total yield 61%).

Reaction of 5-*Vinyluracil* (**5**) *with Phenol*.—Compound (**5**) (90 mg, 0.65 mmol) and phenol (1.2 g, 13 mmol) were dissolved in trifluoroacetic acid (40 ml) and the solution kept at *ca.* 20 °C for 16 h. The solvent was removed by evaporation to give a red oil which was triturated with ether to remove phenol. The white residue was crystallised from aqueous ethanol to give a white solid (130 mg, 86% yield) which was homogeneous by t.l.c. in several solvent systems but whose n.m.r. spectrum showed it to be a mixture of 5-[1-(hydroxyphenyl)ethyl]uracils (Found: C, 60.0; H, 5.0; N, 11.6. $C_{12}H_{12}N_2O_3 \cdot 0.5H_2O$ requires C, 59.7; H, 5.4; N, 11.6%); $\lambda_{max.}$ 267 nm (ε 9 560) in water, pH 6; $\lambda_{max.}$ 277 nm (ε 9 240) in water, pH 13; δ 1.36 (3 H, d, CH_3CH), 3.82 (1 H, q, CH_3CH), 6.56—7.06 (6 H, m, 6-H, phenyl OH, phenyl H), 10.52 (1 H, brs, NH), and 10.90 (1 H, brs, –NH); *m/z* (e.i.) 232 (M^+) and 217 ($M^+ - CH_3$).

Reaction of 2′-*Deoxy*-5-*vinyluridine* (**1**) *with Butan*-1-*ol*.—(*a*) A saturated solution of hydrogen chloride in butan-1-ol (100 ml) was added to a solution of (**1**) (415 mg, 1.6 mmol) in dioxane (150 ml) at 75 °C and the mixture maintained at 75 °C for 1 h. The solution was then evaporated to dryness and the residue fractionated by column chromatography. The column was eluted with chloroform–methanol (6:1). The fractions containing the major component were collected and evaporated to dryness to give 5-(1-butoxyethyl)uracil (**13**) as a white powder (50 mg, 15%) (Found: C, 56.9; H, 7.7; N, 13.4. $C_{10}H_{16}N_2O_3$ requires C, 56.6; H, 7.6; N, 13.2%); $\lambda_{max.}$ 264 nm (ε 10 240) in water, pH 1; $\lambda_{max.}$ 284 nm (ε 8 970) in water, pH 13; δ 0.82

[3 H, t, $O(CH_2)_3CH_3$], 1.05—1.56 (7 H, m, $CHCH_3$, $OCH_2(CH_2)_2CH_3$], 3.28 (2 H, t, OCH_2), 4.23 (1 H, q, $CHCH_3$), 7.14 (1 H, s, 6-H), and 10.8 (2 H, brs, NH).

(*b*) Compound (**1**) (800 mg, 3.1 mmol) was added to a mixture of butan-1-ol (120 ml) and trifluoroacetic acid (25 ml) and the mixture stirred at 55 °C for 7 days. It was then evaporated to give a residual yellow oil which was fractionated by column chromatography. The column was eluted with chloroform–methanol (6:1), appropriate fractions being collected and evaporated to dryness to give 5-(1-*butoxyethyl*)-2′-*deoxyuridine* (**14**) as a colourless glass (150 mg, 15%) (Found: C, 51.9; H, 7.5; N, 7.9. $C_{15}H_{20}N_2O_6 \cdot H_2O$ requires C, 52.0; H, 7.6; N, 8.1%); $\lambda_{max.}$ 267 nm (ε 11 230) in water, pH 1; $\lambda_{max.}$ 266 nm (ε 9 350) in water, pH 13; δ 0.86 [3 H, t, $O(CH_2)_3CH_3$], 1.2—1.6 [7 H, m, $CHCH_3$, $OCH_2(CH_2)_2CH_3$], 2.13 (2 H, m, 2′-H), 3.35 (2 H, t, OCH_2), 3.55 (2 H, m, 5′-H), 3.80 (1 H, m, 4′-H), 4.25 (2 H, m, 3′-H, $CHCH_3$), 4.90 (1 H, t, 5′-OH), 5.20 (1 H, d, 3′-OH), 6.17 (1 H, t, 1′-H), 7.73 (1 H, s, 6-H), 11.0 (1 H, brs, –NH); *m/z* (c.i.) 329 ($M^+ + H$).

Reaction of 2′-Deoxy-5-vinyluridine (**1**) *with Phenol.*—A mixture of compound (**1**) (1.2 g, 8.7 mmol) and phenol (6.4 g, 68 mmol) in 1M hydrochloric acid (180 ml) was heated at 100 °C for 1 h. The solvent was removed by evaporation and the residue repeatedly co-evaporated with water in order to remove the phenol. The resulting brown residue was fractionated by column chromatography, the column being eluted with chloroform–methanol (6:1). Two nucleoside fractions were obtained. Each fraction was purified by column chromatography using the same eluant. The faster-running fraction was isolated as a white amorphous solid (300 mg, 18% yield) which was probably a mixture of 2′-deoxy-5-[1-(2-hydroxyphenyl)-ethyl]uridine (**15**) and 2′-deoxy-5-(1-(3-hydroxyphenyl)ethyl)-uridine (**16**); $\lambda_{max.}$ 268 nm (ε 11 000) in water, pH 1; $\lambda_{max.}$ 237 nm (ε 15 380), λ_{sh} 261 nm (ε 8 800), λ_{sh} 287 nm (ε 3 700) in water, pH 13; δ 1.32 (3 H, d, $CHCH_3$), 2.20 (2 H, m, 2′-H), 3.50 (2 H, m, 5′-H), 3.80 (1 H, m, 4′-H), 4.22 (2 H, m, 3′-H, $CHCH_3$), 5.01 (1 H, m, 5′-OH), 5.29 (1 H, d, 3′-OH), 6.22 (1 H, m, 1′-H), 6.65—6.80 (2 H, m, phenyl H), 6.92—7.05 (2 H, m, phenyl H), 7.61 (0.2H, s, 6-H), 7.66 (0.8H, s, 6-H), 9.35 (1 H, s, phenyl OH), and 11.26 (1 H, s, NH).

The slower-running fraction was obtained as a white solid (260 mg, 16% yield) and shown to be 2′-*deoxy*-5-[1-(4-*hydroxyphenyl*)*ethyl*]*uridine* (**17**) (Found: C, 55.7; H, 5.9; N, 7.4. $C_{17}H_{20}N_2O_6 \cdot H_2O$ requires C, 55.7; H, 6.05; N, 7.65%); $\lambda_{max.}$ 268 nm (ε 10 700) in water, pH 1; $\lambda_{max.}$ 237 nm (ε 15 310), λ_{sh} 260 nm (ε 8 770), λ_{sh} 287 nm (ε 3 650) in water, pH 13; δ 1.35 (3 H, d, $CHCH_3$), 2.13 (2 H, m, 2′-H), 3.58 (2 H, m, 5′-H), 3.82 (1 H, m, 4′-H), 3.88 (1 H, q, $CHCH_3$), 4.27 (1 H, m, 3′-H), 5.13 (1 H, m, 5′-OH), 5.28 (1 H, m, 3′-OH), 6.21 (1 H, t, 1′-H), 6.65 (2 H, d, phenyl 2-H, phenyl 6-H), 7.01 (2 H, d, phenyl 3-H, phenyl 5-H), 7.80 (1 H, s, 6-H), 9.17 (1 H, s, phenyl OH), and 11.23 (1 H, s, NH); [Found: *m/z* (e.i.) 348.1326. $C_{17}H_{20}N_2O_6$ requires M^+, 348.1322].

2′-*Deoxy*-5-[1-(2-*hydroxy*-5-*propan*-2-*ylphenyl*)*ethyl*]*uridine* (**18**).—Compound (**1**) (1.0 g, 7.2 mmol) and 4-propan-2-ylphenol (10.0 g, 73 mmol) were added to a mixture of 1M aqueous trifluoroacetic acid (200 ml) and dioxane (60 ml) and the mixture boiled under reflux for 45 min. It was then cooled, and evaporated to dryness, and the residue co-evaporated with toluene and then fractionated by column chromatography. Chloroform–methanol (6:1) was used as eluant and two columns were required to give the *product* as a white amorphous solid (690 mg, 45% yield) (Found: C, 60.2; H, 6.9; N, 7.0. $C_{20}H_{26}N_2O_6 \cdot 0.5H_2O$ requires C, 60.1; H, 6.8; N, 7.0%); $\lambda_{max.}$ 271 nm (ε 9 410) in water, pH 1; $\lambda_{max.}$ 218 nm (ε 18 250), λ_{sh} 257 nm (ε 8 410), λ_{sh} 290 nm (ε 5 660) in water, pH 13; δ 1.10 (6 H, d, $CH(CH_3)_2$, 1.30 (3 H, m, $CHCH_3$), 2.70 [1 H, m, $CH(CH_3)_2$], 3.40 (2 H, m, 5′-H), 3.75 (1 H, m, 4′-H), 4.15 (2 H, m, 3′-H), $CHCH_3$), 4.50 (2 H, m, 3′-OH, 5′-OH), 6.15 (1 H, t, 1′-H), 6.70 (1 H, m, phenyl 3-H), 6.85 (2 H, m, phenyl 4-H, phenyl 6-H), and 7.50 (1 H, 2 s, 6-H), and 11.15 (1 H, s, NH) (Found: *m/z* (e.i.) 390.1782. $C_{20}H_{26}N_2O_6$ requires M^+, 390.1790).

2′-*Deoxy*-5-(1,2-*dihydroxyethyl*)*uridine* (**19**).—Compound (**1**) (800 mg, 3.1 mmol) and *m*-chloroperbenzoic acid (830 mg, 4.81 mmol) were added to a mixture of tetrahydrofuran (35 ml) and water (50 ml) and the suspension heated at 70 °C for 18 h. The mixture was evaporated to dryness and the residue fractionated by column chromatography. The column was eluted with chloroform–methanol (25—50% methanol, increasing stepwise). The fractions containing the most polar component were evaporated to dryness to give the *product* as a white solid (725 mg, 85% yield); $\lambda_{max.}$ 267 nm (ε 9 050) in water, pH 6; δ 2.10 (2 H, m, 2′-H), 3.3—3.5 [2 H, m, $CH(OH)CH_2OH$], 3.60 (2 H, m, 5′-H), 3.85 (1 H, m, 4′-H), 4.30 (1 H, m, 3′-H), 4.50 [1 H, t, $CH(OH)CH_2OH$, on addition of D_2O], 4.5—5.5 [4 H, m, 3′-OH, 5′-OH, $CH(OH)CH_2OH$], 6.20 (1 H, t, 1′-H), 7.70 (1 H, s, 6-H), and 11.05. (1 H, s, NH); *m/z* (f.a.b.) 289 ($M^+ + 1$) and 173 (Base$^+ + 1$).

5-(1,2-*Diacetoxyethyl*)-3′,5′-*di*-O-*acetyl*-2′*deoxyuridine* (**20**).—Compound (**19**) (52 mg, 0.18 mmol) was dissolved in dry pyridine (5 ml) and acetic anhydride (0.15 ml, 1.5 mmol) was added. After 2 days at *ca.* 20 °C the solvent was evaporated off and the residue co-evaporated with toluene. The residual solid was triturated with water, filtered off, and dried to give the *product* as a white powder (65 mg, 85% yield) (Found: C, 50.0; H, 5.3; N, 6.4. $C_{19}H_{24}N_2O_{11}$ requires C, 50.0; H, 5.3; N, 6.1%); $\lambda_{max.}$ 264 nm (ε 11 700) in ethanol; δ($CDCl_3$) 1.8—2.6 (14 H, m, 2′-H, 4 CH_3CO_2), 4.2—4.5 [5 H, m, 4′-H, 5′-H, CH(OAc)-CH_2OAc], and 5.25 (1 H, m, 3′-H), 5.90 [1 H, 2 t, $CH(OAc)CH_2OAc$], 6.30 (1 H, 2t, 1′-H), 7.60 (1 H, d, 6-H), and 9.55 (1 H, brs, –NH).

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References

1 Y. C. Cheng, B. A. Domin, R. A. Sharma, and M. Bobek, *Antimicrob. Agents and Chemother.*, 1976, **10**, 119.
2 E. De Clercq, J. Descamps, G. Verhelst, R. T. Walker, A. S. Jones, P. F. Torrence, and D. Shugar, *J. Infect. Dis.*, 1980, **41**, 563.
3 E. De Clercq, J. Balzarini, P. F. Torrence, M. P. Mertes, C. L. Schmidt, D. Shugar, P. J. Barr, A. S. Jones, G. Verhelst, and R. T. Walker, *Mol. Pharmacol.*, 1981, **19**, 321.
4 J. J. Cassiman, E. De Clercq, A. S. Jones, R. T. Walker, and H. Van Den Berghe, *Brit. Med. J.*, 1981, **283**, 817.
5 E. T. J. Chelton, C. H. Evans, A. S. Jones, and R. T. Walker, *Biochim. Biophys. Acta*, 1973, **312**, 38.
6 A. S. Jones and R. T. Walker, *Nucleic Acids Res.*. Special Publication No. 1, 1975 s1.
7 E. T. J. Chelton, A. S. Jones, and R. T. Walker, *Biochem. J.*, 1979, **181**, 783.
8 E. T. J. Chelton, M. Duggan, R. N. Hunston. A. S. Jones, M. K. O'Leary, D. J. Overton, and R. T. Walker, *Biochem. J.*, 1980, **187**, 257.
9 K. K. Gauri and G. Malorny, *Arch. Pharmakol. Exp. Pathol.*, 1967, **257**, 21.
10 E. De Clercq and D. Shugar, *Biochem. Pharmacol.*, 1975, **24**, 1073.
11 K. M. Swierkowska, J. D. Jasinaka, and J. A. Steffen, *Biochem. Pharmacol.*, 1973, 22, 85.

12 E. Matthes, D. Bärwolff, P. Preussel, and P. Langen, 'Antimetabolites in Biochemistry, Biology and Medicine,' eds. J. Skoda and P. Langen, Pergamon, Oxford and New York, 1979, p. 115.
13 C. H. Evans, A. S. Jones, and R. T. Walker, *Tetrahedron*, 1974, **29**, 1611.
14 J. H. Dewar and G. Shaw, *J. Chem. Soc.*, 1961, 3254.
15 R. L. Lipnick and J. D. Fissekis, *Bio-org. Chem.*, 1977, **6**, 103.
16 A. S. Jones, M. J. McClean, M. J. Slater, R. T. Walker, J. Balzarini, and E. De Clercq, *J. Chem. Soc., Perkin Trans. 1*, 1987, 457.

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