Synthesis of 5-(1-Substituted Ethyl)uracil Derivatives and Some of their Chemical and Biological Properties

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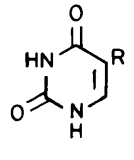
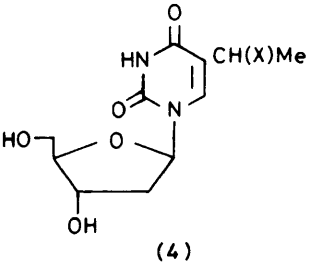
In order to obtain compounds which would give 2'-deoxy-5-vinyluridine (VdUrd) by elimination under basic conditions, a series of 5-(1-substituted ethyl)uracil derivatives has been made. Attempts to obtain 5-(1-alkyl- or -aryl-sulphonyloxy) derivatives were unsuccessful because elimination to give the 5-vinyl derivatives was extremely easy. 5-(1-Acyloxyethyl) derivatives did not eliminate, but with aqueous alkali gave 5-(1-hydroxyethyl)uracil derivatives. Reaction of VdUrd with a series of arenethiols gave 5-(1-arylthioethyl)-2'-deoxyuridines. In the absence of radical inhibitors 5-(2-arylthioethyl)-2'-deoxyuridines were the major products. The arylthio compounds were oxidized to the corresponding sulphoxides and sulphones. Treatment of these 5-(1-substituted) derivatives with potassium t-butoxide in dimethylformamide gave VdUrd. As expected the reaction rate was greatest with the compound which had the best leaving group. However, with aqueous alkali the compounds gave 2'-deoxy-5-(1-hydroxyethyl)uridine and at pH 7.6 at 37 °C they were stable. When N-3 of the uracil ring was alkylated the elimination was faster. The implication of this result for the mechanism of the elimination is discussed. Two of the compounds synthesized, namely 2'-deoxy-5-[1-(2,4,5-trichlorophenylthio)-ethyl]uridine and 2'-deoxy-3-methyl-5-[1-(2,4,5-trichlorophenylthio)ethyl]uridine, showed activity against vaccinia virus and murine L1210 leukaemia cells at a concentration of 30—40 μg/ml, and 2'-deoxy-5-[(2-phenylthio)ethyl]uridine, had activity against different strains of herpes simplex viruses types 1 and 2 at a concentration of 20 μg/ml.

2'-Deoxy-5-vinyluridine (VdUrd) is a potent antiviral and antileukaemic agent in tissue culture [1–3] and has been shown to induce damage to chromosomes.[4] VdUrd Units are incorporated into the DNA of certain micro-organisms which have been grown in the presence of 5-vinyluracil.[5–7] However, in mice, VdUrd is inactive as an antiviral, antileukaemic, or cytotoxic agent.[8] This lack of activity has been attributed to the *in vivo* degradation by the enzyme thymidine phosphorylase. In order to avoid this degradation the synthesis of 5-substituted derivatives of 2'-deoxyuridine which contain a flexible side chain (such compounds are known to be poor substrates for thymidine phosphorylase and inhibitors of uridine phosphorylase [9,10]) and which might be converted into VdUrd in living cells has been attempted. It was hoped that such compounds might show also greater selectivity than VdUrd.

5-Vinyluracil (**1**) can be synthesized from 5-(1-hydroxyethyl)-uracil (**2**) by the action of mesyl chloride under basic conditions.[11] The reaction presumably proceeds *via* the mesyl ester (**3**). Although there is some evidence that this compound is formed, it is too unstable to be isolated. It appeared, therefore, that if we could synthesize compounds of the general structure (**4**), where X is a poorer leaving group than mesyl, they might prove to be precursors of VdUrd in living cells.



(**1**) R = $CH{=}CH_2$
(**2**) R = CH(OH)Me
(**3**) R = CH(OMs)Me



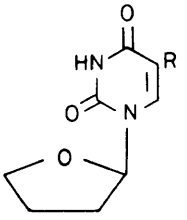
(**4**)

Ms = $S(O)_2Me$

Results and Discussion

Initially it was decided to make X an acyloxy group and, in order to avoid complications with regard to blocking groups on the sugar residue, 1-(tetrahydrofuran-2-yl)uracil derivatives were used instead of 2'-deoxyribonucleosides. Therefore, 5-acetyluracil was converted into its trimethylsilyl derivative which was then condensed with 2-chlorotetrahydrofuran to give 5-acetyl-1-(tetrahydrofuran-2-yl)uracil (**5**), which was reduced with sodium borohydride to 5-(1-hydroxyethyl)-1-(tetrahydrofuran-2-yl)uracil (**6**). The latter was presumably a mixture of diastereoisomers although the n.m.r. signals were not sufficiently different to be resolved at 100 MHz. Treatment of the alcohol (**6**) with mesyl chloride in *N*-methylmorpholine gave 1-(tetrahydrofuran)-2-yl)-5-vinyluracil (**7**). [The characteristic pattern of the vinylic protons is apparent in the n.m.r. spectrum although one of the doublets due to the proton of the $=CH_2$ *cis* to the ring is obscured by the C-2 proton of the tetrahydrofuran ring.] As with the formation of 5-vinyluracil itself, the intermediate mesyl ester could not be isolated. Acetylation of the alcohol (**6**) with acetic anhydride in pyridine gave 5-(1-acetyoxyethyl)-1-(tetrahydrofuran-2-yl)uracil (**8**). [In this compound the chemical shifts of the protons of the diastereoisomers allowed partial resolution at 100 MHz.] Compound (**8**) was treated with *N*-methylmorpholine in dimethylformamide (DMF) at 100 °C but no reaction occurred. Treatment with potassium t-butoxide in the same solvent at 20 °C for 30 min gave the alcohol (**6**) as the only product. Thus, it appears that the acetoxy group does not eliminate but undergoes nucleophilic attack at the carbonyl group. It was felt that if nucleophilic attack could be prevented from occurring at the carbonyl group then the desired elimination might occur. As the carbonyl carbon of pivalate esters is much more sterically hindered then that in acetate, the pivalate ester (**9**) was prepared by treatment of compound (**6**) with pivaloyl chloride in the presence of triethylamine and *NN*-dimethylaminopyridine (DMAP). The product (**9**) was subjected to treatment under

a variety of basic conditions but in no case was any vinyl derivative formed. When reaction did occur, the product was always the hydroxy compound (**6**).



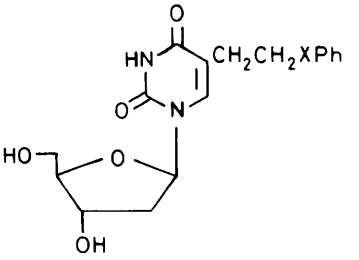
(**5**) R = Ac
(**6**) R = CH(OH)Me
(**7**) R = CH=CH$_2$
(**8**) R = CH(OAc)Me
(**9**) R = CH(OCOCMe$_3$)Me

In view of these results, the possibility of making sulphonate esters of the alcohol (**6**) which might be less reactive than the mesyl ester was investigated. These were toluene-*p*-sulphonate, *p*-methoxybenzenesulphonate, benzenesulphonate, and 2,4,6-triisopropylbenzenesulphonate. In none of these cases could the sulphonate ester be isolated, and the product was always the vinyl derivative.(**7**).

As neither acyl nor sulphonate esters of 5-(1-hydroxyethyl)-uracil derivatives were satisfactory for our purpose, attention was focussed on a study of the products obtained by reaction of thiols with VdUrd. In this case the 2′-deoxyribonucleoside could be used because it was not necessary to protect the hydroxy groups. VdUrd was obtained by decarboxylation of (*E*)-5-(2-carboxyvinyl)-2′-deoxyuridine by heating it with triethylamine in DMF. This method, which has been described previously,[1,2] was modified by addition of a small amount of water to the reaction mixture, thus improving the yield from 24 to 58%.

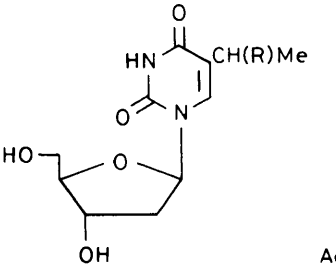
Reaction of VdUrd with thiophenol in hydrochloric acid and acetonitrile gave 2′-deoxy-5-(2-phenylthioethyl)uridine (**10**). The yield of this product was variable, but the addition of a radical initiator (2,2′-azoisobutyronitrile; AIBN) gave a consistent yield of 52%. A similar reaction was carried out on 5-vinyluracil to give 5-(2-phenylthioethyl)uracil (**11**). In order to obtain the required 5-(1-substituted ethyl)derivatives a radical inhibitor, bis-(4-hydroxy-5-methyl-3-t-butylphenyl) sulphide, was used. Under these conditions 2′-deoxy-5-(1-phenylthioethyl)uridine (**12**) was obtained in 85% yield. Using similar conditions the following compounds were prepared: 5-[1-(3-chlorophenylthio)ethyl]-2′-deoxyuridine (**13**), 2′-deoxy-5-[1-(4-nitrophenylthio)ethyl]uridine (**14**), 2′-deoxy-5-[1-(2,4,5-trichlorophenylthio)ethyl]uridine (**15**), 2′-deoxy-5-[1-(2,3,5,6-tetrafluorophenylthio)ethyl]uridine (**16**), and 2′-deoxy-5-[1-(2-methoxyphenylthio)ethyl]uridine (**17**). Reaction of VdUrd with 2-amino(thiophenol) in a similar way and then acetylation followed by treatment with methanolic ammonia gave 5-[1-(2-acetamidophenylthio)ethyl]-2′-deoxyuridine (**18**).

The structures of compound (**10**)—(**18**) were established by elemental analysis and n.m.r. spectroscopy. Each of the products (**12**)—(**18**) was a mixture of diastereoisomers. Thus in the ^{1}H n.m.r. spectrum of compound (**12**) there was complete resolution of two 6-H protons (ratio 1:1), and many other signals, such as the pair of overlapping doublets for the methyl side chain, were partially resolved. Similar evidence for the presence of diastereoisomers was present in the n.m.r. spectra



(**10**) X = S
(**19**) X = SO$_2$
(**21**) X = SO

(**11**)



(**12**) R = SPh
(**13**) R = S–C$_6$H$_4$–Cl
(**14**) R = S–C$_6$H$_4$–NO$_2$
(**15**) R = S–C$_6$H$_2$Cl$_3$
(**16**) R = S–C$_6$HF$_4$
(**17**) R = S–C$_6$H$_4$–MeO
(**18**) R = S–C$_6$H$_4$–NHAc
(**20**) R = S(O)$_2$Ph
(**22**) R = S(O)Ph
(**23**) R = S(O)$_2$–C$_6$H$_4$–Cl
(**24**) R = S(O)$_2$–C$_6$H$_4$–MeO
(**25**) R = S(O)–C$_6$H$_4$–MeO

of the other compounds, although in some [particularly (**14**)] separate signals were not resolved.

The addition reactions of thiols to VdUrd were carried out in the presence of hydrogen chloride but in no case was any 5-(1-chloroethyl)-2′-deoxyuridine detected as a product. All attempts to obtain this compound failed. In reactions which might be expected to give it, the product was either VdUrd or 2′-deoxy-5-(1-hydroxyethyl)uridine.

Oxidation of sulphides (**10**) and (**12**) with *m*-chloroperbenzoic acid (MCPBA) gave the corresponding sulphones (**19**) and (**20**), the latter being a mixture of diastereoisomers. Oxidation of sulphides (**10**) and (**12**) with sodium periodate gave the sulphoxides (**21**) and (**22**), and the sulphones (**23**) and (**24**) were obtained by the oxidation of sulphides (**13**) and (**17**), respectively, with MCPBA. Attempts to obtain sulphones from sulphides (**14**) and (**15**) by a similar oxidation gave a mixture of unidentified products. Compounds (**14**), (**15**), and (**16**) appeared to be resistant to oxidation with sodium periodate, but sulphide (**17**) gave the sulphoxide (**25**). All these sulphoxides and sulphones were mixtures of diastereoisomers. They were characterized by elemental analysis and n.m.r. spectroscopy.

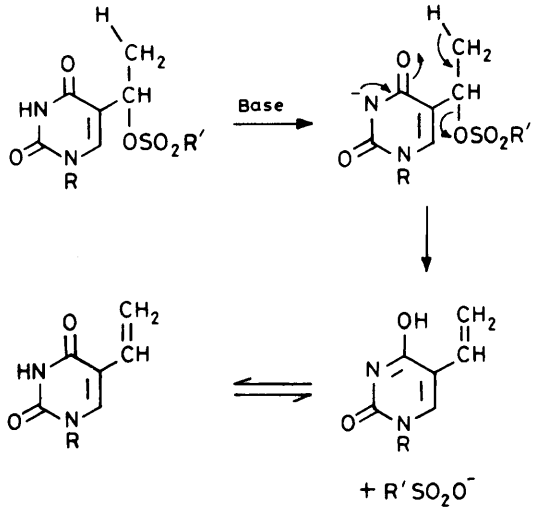
The 5-(1-substituted ethyl)-2′-deoxyuridines [compounds (**12**)—(**18**), (**20**), and (**22**)—(**25**)] were investigated as possible precursors of VdUrd by studying their reactions under basic conditions. Upon treatment with potassium t-butoxide in DMF all of the compounds except (**17**), (**18**), (**24**), and (**25**) gave a

product which co-ran with VdUrd on t.l.c. and had an identical u.v. spectrum with that of VdUrd. Compounds (**13**)—(**16**), (**20**), (**22**), and (**23**) all reacted smoothly at 37 °C to give VdUrd (*ca.* 40—70% after 3 days). The nitro derivative (**14**) produced one, and the sulphoxide (**22**) produced two, additional products. Compound (**12**) required a temperature of 90 °C in order to induce elimination, and under these conditions four additional products were formed. The rate of elimination was found to be faster with the better leaving groups [*e.g.* in compounds (**16**) and (**23**)]. Elimination took place when less than one equivalent of potassium t-butoxide was used but not in DMF in the absence of base.

In 0.1M-aqueous sodium hydroxide, compounds (**12**)—(**16**), (**20**), (**22**), and (**23**) gave a single product which co-ran with 2′-deoxy-5-(1-hydroxyethyl)uridine upon t.l.c. and had an identical u.v. spectrum. All these reactions proceeded smoothly over a period of 7 days at 37 °C, with the exception of that of compound (**12**) which required a higher temperature. In phosphate buffer, pH 7.6 at 37 °C, none of the compounds produced VdUrd. The only product was 2′-deoxy-5-(1-hydroxyethyl)uridine and in the most favourable case it only amounted to ~0.2% of the material after treatment for 4 days.

It appeared, therefore, that in the series of compounds of the general structure (**4**) which were studied, three situations appertain. The first is the case of the sulphonate esters which eliminate so readily to give VdUrd (under both aqueous and non-aqueous conditions) that they could not be isolated. The second case is that of the acyl esters which do not eliminate but which hydrolyse to give the corresponding 5-(1-hydroxyethyl)-derivatives. The third is the case of the sulphides, sulphoxides, and sulphones, most of which eliminate to give VdUrd under non-aqueous conditions, but which are hydrolysed in strongly basic aqueous conditions. No compound was obtained which gives VdUrd under physiological conditions.

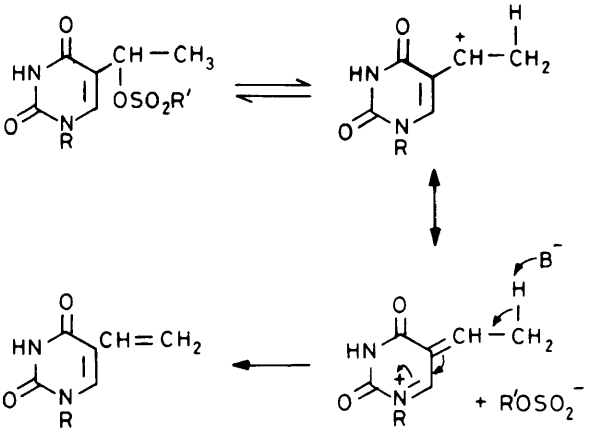
Two probable mechanisms may be postulated for the ready elimination which occurs with sulphonate esters of 5-(1-hydroxyethyl)uracil derivatives (Schemes 1 and 2).



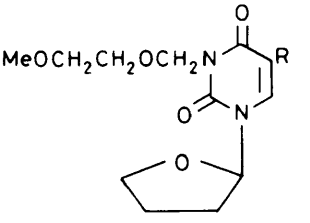
Scheme 1.

In order to distinguish between these two possibilities, compound (**6**) was treated with (2-methoxyethoxy)methyl chloride to give 5-(1-hydroxyethyl)-3-[(2-methoxyethoxy)-methyl)-1-(tetrahydrofuran-2-yl)uracil (**26**). This was treated with mesyl chloride in *N*-methylmorpholine under the usual conditions. Only one product was detected and this was identified as the vinyl derivative (**27**).

This result indicated that the elimination was not dependent



Scheme 2.

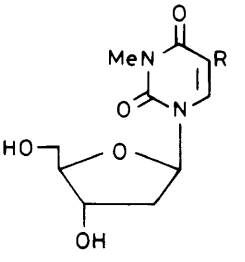


(**26**) R = CH(OH)Me

(**27**) R = CH=CH$_2$

on the formation of an anion at N-3, and therefore favours Scheme 2. A similar result was obtained in the case of the sulphide (**15**). This, upon treatment with methyl iodide, gave 2′-deoxy-3-methyl-5-[1-(2,4,5-trichlorophenylthio)ethyl]-uridine (**28**). As the product of elimination from this compound should be 2′-deoxy-3-methyl-5-vinyluridine (**29**), the latter was synthesized by the action of methyl iodide on VdUrd. Comparison of the rates of elimination with potassium t-butoxide in DMF at 37 °C showed that after 50 min sulphide (**15**) had eliminated to the extent of 5% whereas sulphide (**28**) had completely eliminated to give compound (**29**). After 6 h compound (**15**) had eliminated to the extent of 45%. These results strongly favour Scheme 2 as opposed to Scheme 1, and indicate that the formation of an anion at N-3 actually retards the elimination.

The compounds synthesized as described above were evaluated for antiviral activity against the DNA viruses herpes



(**28**) R = CHMe(Cl)S(2,4,5-trichlorophenyl)

(**29**) R = CH=CH$_2$

Table. Antiviral and antitumour-cell activity of 5-(1-substituted ethyl)uracil derivatives

Compound	MIC_{50} (μg/ml)[a] HSV-1	HSV-2	VV	VSV	ID_{50} (μg/ml)[a] L1210
(10)	20	20	>400	>400	480
(11)	>100	>100	>100	>100	>1 000
(12)	>100	>100	300	400	525
(13)	>100	>100	>100	>100	>100
(14)	>400	>400	150	>400	240
(15)	>100	>100	40	>100	31
(16)	>200	>400	300	>200	280
(17)	>400	>400	>400	>400	>1 000
(18)	>400	>400	>400	>400	470
(19)	>400	>400	>400	>400	⩾1 000
(20)	100	>400	300	>400	>1 000
(21)	>100	>100	150	>400	>1 000
(22)	2	7	20	>400	33
(23)	>200	>200	200	>200	>100
(24)	>400	>400	>400	>400	>1 000
(28)	>100	>100	40	>100	32
(29)	>200	>100	>200	>200	>1 000
VdUrd	0.02	0.1	0.2	>400	2.4[c]
(2′-Deoxy-5-vinyluridine)	0.02[b]	0.1[b]	0.4[b]		
BVdUrd	0.02	7	7	>400	27[c]
[(*E*)-5-(2-bromovinyl)-2′-Deoxyuridine]	0.008[b]	1[b]	7[b]		
EtdUrd	0.3	0.4	2	>400	8.5[c]
(2′-Deoxy-5-ethyluridine)	0.5[b]	0.3[b]	1[b]		

[a] For abbreviations, see text. For HSV-1, similar values were obtained with three HSV-1 strains (KOS, F, and McIntyre); for HSV-2, similar values were obtained with three HSV-2 strains (G, 196, and Lyons). [b] Data taken from ref. 2. [c] Data taken from ref. 3.

simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), vaccinia virus (VV), and the RNA (rhabdo) virus vesicular stomatitis virus (VSV) in primary rabbit kidney (PRK) cells, and for antitumour-cell activity against murine leukaemia (L1210) cells. The antiviral activity is expressed as MIC_{50}, or minimum inhibitory concentration required to reduce virus-induced cytopathogenicity by 50%; the antitumour-cell activity is expressed as ID_{50}, or 50% inhibitory dose; *i.e.* the concentration required to inhibit the number of cells, during their expontential growth phase, by 50%.

For the tetrahydrofuranyl derivatives (**5**)—(**9**), (**26**), and (**27**), no marked antiviral or antitumour-cell activity was noted (MIC_{50} > 100 μg/ml; ID_{50} > 300 μg/ml). Of the other compounds, only (**10**), (**15**), (**22**), and (**28**) showed a distinct inhibitory effect on virus-induced cytopathogenicity or tumour-cell proliferation (Table).

The antiviral and antitumour-cell activity of compound (**22**) may be attributed to the slow decomposition of the compound (which was an amorphous mixture of diastereoisomers) in the solid state to produce *ca.* 1% of VdUrd.

Compound (**10**) was specifically active against HSV-1 and HSV-2, but only at a relatively high MIC_{50} (20 μg/ml). Compounds (**15**) and (**28**), which both contain a 2,4,5-trichlorophenylthio group, showed activity against L1210 cell growth and vaccinia virus-induced cytopathogenicity, but, again, only at a relatively high concentration (30—40 μg/ml).

Experimental

N.m.r. spectra were recorded on a 100 MHz Varian XL100 spectrometer with $(CD_3)_2SO$ as the solvent unless otherwise stated. U.v. spectra were measured on a Perkin-Elmer 552 spectrophotometer for ethanol solutions unless otherwise stated. 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, West Germany). All reactions were carried out under scrupulously dry conditions unless otherwise indicated, and solvents were evaporated off under reduced pressure on work-up.

5-*Acetyl*-1-(*tetrahydrofuran*-2-*yl*)*uracil* (**5**).—A suspension of 5-acetyluracil (2.24 g, 10 mmol) in hexamethyldisilazane (15 ml) containing trimethylsilyl chloride (0.15 ml) was boiled under reflux until complete solution was achieved. The solution was evaporated under reduced pressure to give the required trimethylsilyl derivative as a clear oil.

Redistilled 2,3-dihydrofuran (792 mg, 11 mmol) was dissolved in methylene dichloride (20 ml) and gaseous HCl was bubbled through the solution for 10 min at ~20 °C. Anhydrous Na_2CO_3 (5 g) was then added and the suspension was stirred at 4 °C for 5 min. A solution of the trimethylsilyl derivative in methylene dichloride (30 ml) was added and the mixture was stirred at ~20 °C for 18 h, then filtered, the insoluble material was washed with methylene dichloride, and the combined filtrate and washings were evaporated to give a solid, which was purified by column chromatography with chloroform–methanol (6:1) as eluant. Appropriate fractions were evaporated to dryness to give title product as a white powder (1.78 g, 66%), m.p. 167—169 °C; $\lambda_{max.}$ (H_2O; pH 1) 229 (ε 7 100), and 291 nm (8 100); $\lambda_{max.}$ (H_2O; pH 13) 295 nm (6 600); δ 1.8—2.3 (4 H, m, 3′- and 4′-H_2), 2.4 (3 H, s, MeCO), 3.8—4.3 (2 H, m, 5′-H_2), 5.8—6.0 (1 H, dd, 2′-H), 8.1 (1 H, s, 6-H), and 11.6 (1 H, s, NH).

5-(1-*Hydroxyethyl*)-1-(*tetrahydrofuran*-2-*yl*)*uracil* (**6**).—To a solution of compound (**5**) (7.0 g, 31 mmol) in 0.1M-aqueous NaOH (200 ml) was added sodium borohydride (3.8 g, 100 mmol) and the solution was kept at ~20 °C in the dark for 2 h [t.l.c. in chloroform–methanol (6:1) showed that no starting material remained]. The reaction mixture was neutralized with 4M-HCl and the water was removed by evaporation. The

residue was purified by column chromatography with chloroform–methanol (6:1) as eluant. Evaporation of the appropriate fractions gave the *title product* (4.94 g, 70%), m.p. 108—110 °C (Found: C, 53.4; H, 6.5; N, 12.6. $C_{10}H_{14}N_2O_4$ requires C, 53.1; H, 6.2; N, 12.4%); $\lambda_{max.}$ (H_2O; pH 6) 268 nm (8 600); δ 1.3 [3 H, d, CH(OH)*Me*], 1.8—2.4 (4 H, m, 3′- and 4′-H_2), 3.7—4.2 (2 H, m, 5′-H_2), 4.5 [1 H, m, C*H*(OH)Me], 5.1 (1 H, d, OH), 5.9 (1 H, dd, 2′-H), 7.4 (1 H, s, 6-H), and 11.3 (1 H, s, NH).

1-(*Tetrahydrofuran-2-yl*)-5-*vinyluracil* (**7**).—To a solution of the alcohol (**6**) (0.24 g, 3.3 mmol) in DMF (10 ml) were added *N*-methylmorpholine (0.36 ml, 3.3 mmol) and methanesulphonyl chloride (0.26 ml, 3.3 mmol) and the solution was kept at 4 °C for 20 h. Then a further amount (0.36 ml) of *N*-methylmorpholine was added and the solution was heated at 100 °C for 30 min. The solution was cooled, 0.1M-aqueous NaOH (35 ml) was added, and the solution was evaporated to afford a gum, which was dissolved in methanol. Silica gel was then added, the suspension was evaporated to dryness, and the solid was suspended in chloroform–methanol (6:1) and applied to the top of a silica gel chromatography column. The column was eluted with the same solvent and appropriate fractions were collected and evaporated to dryness to give the *title product* as a white solid (0.50 g, 73%), m.p. 131—133 °C (Found: C, 56.2; H, 5.8; N, 12.7. $C_{10}H_{12}N_2O_3 \cdot 0.33H_2O$ requires C, 56.1; H, 6.0; N, 13.1%); $\lambda_{max.}$ (H_2O; pH 6) 237 (12 000) and 287 nm (9 100); δ 1.8—2.4 (4 H, m, 3′-and 4′-H_2), 3.7—4.3 (2 H, m, 5′-H_2), 5.1 (1 H, dd, vinyl H), 5.9—6.1 (2 H, m, 2′-H and vinyl H), 6.3—6.6 (1 H, dd, vinylic H), 7.6 (1 H, s, 6-H), and 11.2 (1 H, s, NH).

5-(1-*Acetoxyethyl*)-1-(*tetrahydrofuran-2-yl*)*uracil* (**8**).—To a solution of the alcohol (**6**) (0.74 g, 3.3 mmol) in pyridine (15 ml) was added acetic anhydride (0.31 ml, 3.3 mmol) and the solution kept at ~ 20 °C for 20 h, and was then evaporated to give an oil, which was dissolved in methylene dichloride (50 ml). The solution was washed successively with 0.1M-HCl (3 × 50 ml) and 0.1M-aqueous $NaHCO_3$ (3 × 50 ml), dried, and then evaporated to give a white solid, which was purified by column chromatography with chloroform as eluant. The *title product* was obtained as a white solid (0.40 g, 45%), m.p. 95—97 °C (Found: C, 53.9; H, 6.0; N, 10.4. $C_{12}H_{16}N_2O_5$ requires C, 53.7; H, 6.0; N, 10.4%); $\lambda_{max.}$ (H_2O; pH 1) 268 nm (7 800); $\lambda_{max.}$ (H_2O; pH 13) 267 nm (4 600); δ($CDCl_3$) 1.4 (3 H, dd, CH*Me*), 1.8—2.2 (7 H, m, 3′- and 4′-H_2 and MeCO), 3.9—4.3 (2 H, m, 5′-H_2), 5.8 [1 H, m, C*H*(OAc)Me], 6.0 (1 H, m, 2′-H), 7.4 (1 H, 2 s, 6-H), and 9.9 (1 H, br d, NH).

5-(1-*Pivaloyloxyethyl*)-1-(*tetrahydrofuran-2-yl*)*uracil* (**9**).—To a solution of compound (**6**) (0.37 g, 1.65 mmol) in methylene dichloride (20 ml) at 0 °C were added DMAP (50 mg, 0.41 mmol) and pivaloyl chloride (0.21 ml, 1.75 mmol). Then a solution of triethylamine (0.26 ml, 1.65 mmol) in methylene dichloride (20 ml) was added dropwise to the stirred mixture at 0 °C during 30 min, and the solution was allowed to warm up to ~ 20 °C and was stirred for a further 60 min. The solution was then evaporated to afford an oil, which was dissolved in acetone, silica gel was added, and the suspension was evaporated to dryness. This solid was then applied to the top of a chromatography column which was eluted with toluene–acetone (3:2). Appropriate fractions were collected and evaporated to dryness to give the *title product* as a white solid (300 mg, 60%), m.p. 126 °C (Found: C, 57.9; H, 7.3; N, 8.8. $C_{15}H_{22}N_2O_5$ requires C, 58.1; H, 7.1; N, 9.0%); $\lambda_{max.}$ 268 nm (10 700); $\lambda_{max.}$ (alkaline ethanol) 268 nm (8 200); δ 1.15 (9 H, s, CMe_3), 1.35 [3 H, d, CH(OPiv)*Me*], 1.8—2.3 (4 H, m, 3′- and 4′-H_2), 3.7—4.2 (2 H, m, 5′-H_2), 5.6 [1 H, q, C*H*(OPiv)Me], 5.9 (1 H, m, 2′-H), 7.4 (1 H, s, 6-H), and 11.4 (1 H, s, NH).

2′-*Deoxy*-5-*vinyluridine* (VdUrd).—A solution of (*E*)-5-(2-carboxyvinyl)-2′-deoxyuridine (4 g, 13.4 mmol) in a mixture of triethylamine (14.3 ml), water (2 ml), and DMF was heated at 105 °C for 24 h. The resulting red solution was evaporated to give an oil, which was purified by column chromatography. The column was eluted with chloroform–methanol (4:1), and appropriate fractions were collected and evaporated to dryness to give a white solid, which was crystallized from chloroform–methanol (1:1) to give the title product as needles (1.97 g, 58%); $\lambda_{max.}$ 237 (11 000) and 290 nm (8 200); $\lambda_{min.}$ 262 nm; δ 2.14 (2 H, m, 2′-H_2), 3.57 (2 H, m, 5′-H_2), 3.77 (1 H, m, 4′-H), 4.24 (1 H, m, 3′-H), 5.13 (3 H, m, vinylic H and 3′- and 5′-OH), 5.86 (1 H, dd, vinylic H), 6.13 (1 H, t, 1′-H), 6.40 (1 H, dd, vinylic H), 8.15 (1 H, s, 6-H), and 11.53 (1 H, br s, NH).

2′-*Deoxy*-5-(2-*phenylthioethyl*)*uridine* (**10**).—To a solution of 2′-deoxy-5-vinyluridine (575 mg, 2.26 mmol) in a mixture of acetonitrile (24 ml) and water (12 ml) were added thiophenol (0.4 ml, 3.9 mmol) and AIBN (40 mg), and the mixture was boiled for 1 h. The solvent was then removed by evaporation and the residue was subjected to column chromatography with chloroform–methanol (6:1) as eluant. The major nucleoside product was isolated, and crystallized from ethanol–diethyl ether to give the *title product* as white needles (424 mg, 52%), m.p. 133 °C (Found: C, 55.7; H, 5.7; N, 7.7. $C_{17}H_{20}N_2O_5S$ requires C, 56.0; H, 5.5; N, 7.7%); $\lambda_{max.}$ 257 nm (14 580); δ 2.05 (2 H, m, 2′-H_2), 2.50 (2 H, t, CH_2CH$_2$SPh), 3.05 (2 H, t, CH$_2$CH_2SPh), 3.55 (2 H, m, 5′-H_2), 3.75 (1 H, m, 4′-H), 4.25 (1 H, m, 3′-H), 4.95 (1 H, t, 5′-OH), 5.20 (1 H, d, 3′-OH), 6.15 (1 H, t, 1′-H), 7.1—7.4 (5 H, m, Ph), 7.70 (1 H, s, 6-H), and 11.25 (1 H, br s, NH).

5-(2-*Phenylthioethyl*)*uracil* (**11**).—To a solution of 5-vinyluracil (565 mg, 4.09 mmol) in a mixture of water (45 ml) and acetonitrile (75 ml) at 80 °C were added thiophenol (0.45 ml, 4.4 mmol) and AIBN (10 mg), and the mixture was kept at 80 °C for 10 min, then filtered while hot, and the filtrate was cooled to give needles (450 mg). Concentration of the mother liquors gave a further batch of crystals (350 mg) to give a total yield of 800 mg (79%) of the *title product*, m.p. 224 °C (Found: C, 58.1; H, 4.7; N, 11.6. $C_{12}H_{12}N_2O_2S$ requires C, 58.05; H, 4.9; N, 11.3%); $\lambda_{max.}$ 255 (9 160) and 289 nm (6 430); $\lambda_{min.}$ (H_2O; pH 13) 276 nm (6 230); δ 2.50 (2 H, t, CH_2CH$_2$SPh), 3.05 (2 H, t, CH$_2$CH_2SPh), 6.0—6.3 (6 H, m, 6-H and Ph), 10.35 (1 H, br s, NH), and 11.70 (1 H, br s, NH).

Method for the Synthesis of 5-(1-*Arylthioethyl*)-2′-*deoxyuridines* (**12**)—(**17**).—2′-Deoxy-5-vinyluridine (VdUrd) was added to a boiling, deoxygenated solution containing 2M-aqueous HCl (33 ml), acetonitrile (66 ml) and bis-(4-hydroxy-5-methyl-3-t-butylphenyl) sulphide (100 mg). The arenethiol was then added and the mixture was heated for another 60 min. The mixture was then cooled, evaporated to dryness, and the residue was co-evaporated with water and then ethanol. The residue was then fractionated by column chromatography with chloroform–methanol (6:1) as eluant. Fractions containing the broad or double nucleoside spot running faster than VdUrd on t.l.c. were pooled, and evaporated to dryness to give the product as a white amorphous solid (unless otherwise stated).

2′-*Deoxy*-5-(1-*phenylthioethyl*)*uridine* (**12**). VdUrd (0.80 g, 3.1 mmol) and thiophenol (1 ml, 9.8 mmol) were used to give the *title product* (980 mg, 85%) (Found: C, 55.9; H, 5.4; N, 7.6. $C_{17}H_{20}N_2O_5S$ requires C, 56.0; H, 5.5; N, 7.7%); δ 1.35—1.5 (3 H, 2 d, Me), 1.9—2.0 (2 H, m, 2′-H_2), 3.5 (2 H, m, 5′-H_2), 3.7 (1 H, m, 4′-H), 4.05—4.35 [2 H, m, 3′-H and C*H*(SPh)Me], 4.9 (1 H, m, 5′-OH), 5.1 (1 H, m, 3′-OH), 6.05 (1 H, m, 1′-H), 7.20 (5 H, m, Ph), 7.60 and 7.70 (1 H, 2 s, 6-H), and 11.20 (1 H, br s, NH).

5-[1-(3-*Chlorophenylthio*)*ethyl*]-2′-*deoxyuridine* (**13**). VdUrd

(290 mg, 1.14 mmol) and 3-chlorothiophenol (200 mg, 1.38 mmol) gave the *title product* (182 mg, 33%) (Found: C, 50.9; H, 5.1; N, 6.7. $C_{17}H_{19}ClN_2O_5S$ requires C, 51.2; H, 4.8; N, 7.0%); $\lambda_{max.}$ 263 nm (14 450); δ 1.5 (3 H, 2 d, Me), 2.0 (2 H, m, 2′-H_2), 3.55 (2 H, m, 5′-H_2), 3.8 (1 H, m, 4′-H), 4.2 (1 H, m, 3′-H), 4.4 [1 H, q, C*H*(SAr)], 5.0 (1 H, m, 5′-OH), 5.2 (1 H, d, 3′-OH), 6.15 (1 H, 2 t, 1′-H), 7.3 (4 H, m, ArH), 7.83 and 7.92 (1 H, 2 s, 6(H), and 11.4 (1 H, br s, NH).

2′-*Deoxy*-5-[1-(4-*nitrophenylthio*)*ethyl*]*uridine* (**14**). VdUrd (1.16 g, 4.75 mmol) and 4-nitrothiophenol (800 mg, 5.2 mmol) were used to give the *title product* (1.06 g, 57%) as a yellow solid (Found: C, 48.1; H, 4.7; N, 9.8. $C_{17}H_{19}N_3O_7S{\cdot}H_2O$ requires C, 47.8; H, 4.95; N, 9.8%); $\lambda_{max.}$ 267 (8 360) and 339 nm (9 830); $\lambda_{min.}$ 298 nm (4 120); δ 1.55 (3 H, d, Me), 2.05 (2 H, m, 2′-H_2), 3.70 (2 H, m, 5′-H_2), 3.80 (1 H, m, 4′-H), 4.26 (1 H, m, 3′-H), 4.64 [1 H, q, C*H*(SAr)], 5.10 (1 H, m, 5′-OH), 5.20 (1 H, m, 3′-OH), 6.10—6.24 (1 H, 2 t, 1′-H), 7.5—7.7 (2 H, m, aryl 2-H and 4-H), 8.05—8.25 (3 H, m, 6-H, and 3-H, and aryl 5-H), and 11.44 (1 H, br s, NH).

2′-*Deoxy*-5-[1-(2,4,5-*Trichlorophenylthio*)*ethyl*]*uridine* (**15**). VdUrd (488 mg, 1.92 mmol) and 2,4,5-trichlorothiophenol (500 mg, 2.3 mmol) were used to give the *title product* (543 mg, 60%) (Found: C, 43.9; H, 3.4; N, 5.8. $C_{17}H_{17}Cl_3N_2O_5S$ requires C, 43.6; H, 3.7; N, 6.0%); $\lambda_{max.}$ 269 nm (12 400); δ 1.55 (3 H, d, Me), 2.10 (2 H, m, 2′-H_2), 3.60 (2 H, m, 5′-H_2), 3.80 (1 H, m, 4′-H), 4.25 (1 H, m, 3′-H), 4.55 [1 H, q, C*H*(SAr)], 5.05 (1 H, m, 5′-OH), 5.20 (1 H, d, 3′-OH), 6.15 (1 H, 2 t, 1′-H), 7.85 and 7.70 (2 H, 2 s, ArH), 8.0 (1 H, s, 6-H), and 11.55 (1 H, br s, NH).

2′-*Deoxy*-5-[1-(2,3,5,6-*tetrafluorophenylthio*)*ethyl*]*uridine* (**16**). VdUrd (1.0 g, 3.9 mmol) and 2,3,5,6-tetrafluorothiophenol (1 ml, 5.0 mmol) were used to give the *title product* (805 mg, 47%) (Found: C, 46.5; H, 3.6; N, 6.1. $C_{17}H_{16}F_4N_2O_5S$ requires C, 46.4; H, 3.7; N, 6.4%); $\lambda_{max.}$ 271 nm (14 160); δ 1.45 (3 H, d, Me), 1.8—2.2 (2 H, m, 2′-H_2), 3.50 (2 H, m, 5′-H_2), 3.77 (1 H, m, 4′-H), 4.20 (1 H, m, 3′-H), 4.35 [1 H, q, C*H*(SAr)], 4.95 (1 H, m, 5′-OH), 5.20 (1 H, m, 3′-OH), 6.10 (1 H, 2 t, 1′-H), 7.70 (1 H, 2 s, 6-H), 7.8—8.1 (1 H, m, ArH), and 11.40 (1 H, br s, NH).

2′-*Deoxy*-5-[1-(2-*methoxyphenylthio*)*ethyl*]*uridine* (**17**). VdUrd (980 mg, 3.9 mmol) and 2-methoxythiophenol (993 mg, 7.1 mmol) were used to give the *title product* (1.4 g, 92%) (Found: C, 54.5; H, 5.5; N, 7.1. $C_{18}H_{22}N_2O_6S$ requires C, 54.8; H, 5.6; N, 7.1%); $\lambda_{max.}$ 270 nm (12 600); δ 1.44 (3 H, 2 d, Me), 2.0 (2 H, m, 2′-H_2), 3.50 (2 H, m, 5′-H_2), 3.80 (4 H, m, 4′-H, and OMe), 4.20 (1 H, m, 3′-H), 4.35 (1 H, 2 q, C*H*(SAr)], 4.98 (1 H, m, 5′-OH), 5.20 (1 H, m, 3′-OH), 6.15 (1 H, 2 t, 1′-H), 6.80—7.05 (2 H, m, aryl 3- and 5-H), 7.25 (2 H, m, aryl 4- and 6-H), 7.62 and 7.70 (1 H, 2 s, 6-H), and 11.30 (1 H, br s, NH).

5-[1-(2-*Acetamidophenylthio*)*ethyl*]-2′-*deoxyuridine* (**18**).—A solution of VdUrd (600 mg, 2.36 mmol) and 2-amino(thiophenol) (600 mg, 2.36 mmol) in 2M-hydrochloric acid (70 ml) was boiled under reflux for 1 h. The mixture was evaporated to dryness and dried over phosphoric anhydride and sodium hydroxide pellets for 18 h. The residue was then dissolved in pyridine (70 ml), acetic anhydride (8 ml) was added, and the solution was kept at ~20 °C for 16 h, then evaporated to dryness, and the residue was co-evaporated with toluene, ethanol, and acetone to give a solid, which was fractionated by column chromatography with chloroform–ethanol (20:1) as eluant. The major nucleoside fraction (R_F ~0.4) containing three u.v.-absorbing components was collected and the solvent was removed by evaporation to give a yellow gum (1.5 g), to which methanol (30 ml) and aqueous ammonia (s.g. 0.88; 30 ml) were added. After 16 h at ~20 °C the solvent was removed by evaporation and the residue was fractionated by column chromatography. The column was eluted with chloroform–ethanol (9:1) followed by chloroform–ethanol (6:1). Appropriate fractions were collected and evaporated to dryness to give the *title product* (363 mg, 37%) as a white solid (Found: C, 54.0; H, 5.6; N, 10.0. $C_{17}H_{23}N_3O_2S$ requires C, 54.15; H, 5.5; N, 9.9%); $\lambda_{max.}$ 253—254 nm (18 800); δ 1.44 (3 H, 2 d, Me), 1.8—2.1 (2 H, m, 2′-H_2), 2.18 (3 H, 2 s, COMe), 3.52 (2 H, m, 5′-H_2), 3.78 (1 H, m, 4′-H), 3.9—4.2 [2 H, m, 3′-H and C*H*(SAr)], 4.95—5.25 (2 H, m, 3′- and 5′-OH), 6.13 (1 H, t, 1′-H), 5.96—7.84 (4 H, m, ArH), 8.12 and 8.20 (1 H, 2 s, 6-H), 9.26 and 9.36 (1 H, 2 s, N*H*COMe), and 11.55 (1 H, br s, NH).

2′-*Deoxy*-5-(2-*phenylsulphonylethyl*)*uridine* (**19**).—A mixture of compound (**10**) (144 mg, 0.39 mmol) and MCPBA (143 mg, 0.83 mmol) in ethanol (27 ml) was stirred at ~20 °C for 18 h. The solvent was then removed by evaporation, and the resulting white solid was fractionated by column chromatography. The column was eluted with chloroform–ethanol (6:1) and appropriate fractions were evaporated to dryness and the residue crystallized from ethanol–ethyl acetate to give the *title product* as white needles (65 mg, 42%), m.p. 148 °C (Found: C, 51.5; H, 5.1; N, 7.0. $C_{17}H_{20}N_2O_7S$ requires C, 51.5; H, 5.1; N, 7.1%); $\lambda_{max.}$ 270 (11 640) and 266 nm (11 680); $\lambda_{min.}$ 268 nm (11 500); δ 2.05 (2 H, m, 2′-H_2), 2.50 (2 H, t, $CH_2CH_2SO_2Ph$), 3.40 (2 H, t, $CH_2CH_2SO_2Ph$), 3.50 (2 H, m, 5′-H_2), 3.70 (1 H, m, 4′-H), 4.20 (1 H, m, 3′-H), 5.0 (2 H, br s, 3′- and 5′-OH), 6.05 (1 H, t, 1′-H), 7.4—7.9 (6 H, m, 6-H and Ph), and 11.20 (1 H, br s, NH).

2′-*Deoxy*-5-(1-*phenylsulphonylethyl*)*uridine* (**20**).—Compound (**12**) (190 mg, 0.52 mmol) was oxidized with MCPBA as described for the preparation of compound (**19**). The isolation procedure was also similar and gave the *title product* (93 mg, 45%) as an amorphous white solid (Found: C, 49.4; H, 5.4; N, 6.7. $C_{17}H_{20}N_2O_7S{\cdot}H_2O$ requires C, 49.3; H, 5.4; N, 6.8%); $\lambda_{max.}$ 272 nm (10 380); δ 1.44 (3 H, d, Me), 2.0—2.2 (2 H, m, 2′-H_2), 3.51 (2 H, m, 5′-H_2), 3.78 and 3.85 (1 H, 2 m, 4′-H), 4.20 and 4.25 (1 H, 2 m, 3′-H), 4.50 [1 H, m, C*H*(SO_2Ar)], 5.08 (1 H, m, 5′-OH), 5.35 (1 H, m, 3′-OH), 6.1 and 6.2 (1 H, 2 t, 1′-H), 7.54—7.78 (5 H, m, Ph), 8.0 and 8.05 (1 H, 2 s, 6-H), and 11.40 (1 H, s, NH).

2′-*Deoxy*-5-(2-*phenylsulphinylethyl*)*uridine* (**21**).—To a solution of compound (**10**) (156 mg, 0.43 mmol) in methanol (20 ml) at 0 °C was added a solution of sodium metaperiodate (95 mg, 0.45 mmol) in water (25 ml) at 0 °C. The mixture was kept at 0 °C for 3 h and then warmed to ~20 °C and stirred for 18 h. The solvent was removed by evaporation, and the solid residue was purified by column chromatography with chloroform–methanol (8:1) as eluant. Appriopriate fractions were collected to give the *title product* as a white solid (144 mg, 91%) (Found: C, 53.4; H, 5.0; N, 7.5. $C_{17}H_{20}N_2O_6S$ requires C, 53.7; H, 5.3; N, 7.4%); $\lambda_{max.}$ 265 nm (10 710); δ 2.05 (2 H, m, 2′-H_2), 2.50 (2 H, t, CH_2CH_2SOPh), 3.0 (2 H, 2 t, CH_2CH_2SOPh), 3.55 (2 H, m, 5′-H_2), 3.70 (1 H, m, 4′-H), 4.20 (1 H, m, 3′-H), 4.90 (1 H, m, 5′-OH), 5.10 (1 H, m, 3′-OH), 6.05 (1 H, t, 1′-H), 7.4—7.6 (5 H, m, Ph), 7.65 (1 H, s, 6-H), and 10.80 (1 H, br s, NH).

2′-*Deoxy*-5-(1-*phenylsulphinylethyl*)*uridine* (**22**).—Compound (**12**) (980 mg, 2.7 mmol) and sodium metaperiodate (526 mg, 2.46 mmol) were dissolved in a mixture of methanol (20 ml) and water (25 ml) at 0 °C. The solution was kept at 0 °C for 18 h and then filtered to remove sodium iodate. The filtrate was evaporated to dryness, methanol (20 ml) was added to the residue, and the resulting suspension was filtered. The filtrate was evaporated to dryness and the residue was subjected to column chromatography with chloroform–ethanol (6:1) as eluant. Pooling the appropriate fractions and evaporation to dryness afforded the *title product* as a white solid (700 mg, 75%) (Found: C, 53.5; H, 5.1; N, 7.2%); $\lambda_{max.}$ 274 nm (10 340); δ 1.1—1.4 (3 H, m, Me), 2.1 (2 H, m, 2′-H_2), 3.6, 3.8, and 4.2 [5 H, 3 m, 3′-H, 4′-H, 5′-H_2, and C*H*(SOPh)], 4.8—5.3 (2 H, m, 3′- and 5′-

OH), 6.2 (1 H, m, 1′-H), 7.3—7.9 (6 H, m, 6-H and Ph), and 11.25 and 11.55 (1 H, 2 br s, NH).

5-[1-(3-*Chlorophenylsulphonyl*)*ethyl*]-2′-*deoxyuridine* (**23**).—To a solution of compound (**13**) (129 mg, 0.32 mmol) in ethanol (15 ml) at 0 °C was added dropwise a solution of MCPBA (130 mg, 0.75 mmol) in ethanol (5 ml) during 10 min. The solution was kept at 4 °C for 18 h and then evaporated to dryness. Diethyl ether was added to the residue, the ether was evaporated off, and the residual white foam was triturated with diethyl ether (10 ml). The ether was decanted off and the remaining solid was purified by column chromatography. The column was eluted with chloroform–methanol (6:1). The appropriate fractions were collected, and evaporated to dryness, and the residue was triturated well with diethyl ether and dried to give the *title product* as a white solid (100 mg, 73%) (Found: C, 46.3; H, 4.4; N, 6.4. $C_{17}H_{19}ClN_2O_7S{\cdot}0.5H_2O$ requires C, 46.4; H, 4.6; N, 6.4%); $\lambda_{max.}$ 274 nm (12 000); δ 1.5 (3 H, d, Me), 2.1 (2 H, m, 2′-H_2), 3.6 (2 H, m, 5′-H_2), 4.85 (1 H, m, 4′-H), 4.25 (1 H, m, 3′-H), 4.55 [1 H, q, C*H*(SO_2Ar)], 5.1 (2 H, br s, 3′- and 5′-OH), 6.12 (1 H, t, 1′-H), 7.5—7.9 (4 H, m, ArH), 8.1 (1 H, d, 6-H), and 11.40 (1 H, br s, NH).

2′-*Deoxy*-5-[1-(2-*methoxyphenylsulphonyl*)*ethyl*]*uridine* (**24**).—A mixture of compound (**17**) (335 mg, 0.85 mmol) and MCPBA (356 mg, 2.1 mmol) in ethanol (50 ml) was stirred at ~20 °C for 18 h. The solvent was then removed by evaporation, and the residue was co-evaporated with diethyl ether and then triturated with diethyl ether (2 × 10 ml). The ether-insoluble residue was purified by column chromatography with chloroform–methanol (8:1) as eluant. Appropriate fractions were collected, and evaporated to dryness, and the residue was triturated with diethyl ether and dried to give the *title product* as a white solid (238 mg, 68%) (Found: C, 50.8; H, 5.3; N, 6.7. $C_{18}H_{22}N_2O_8S$ requires C, 50.7; H, 5.2; N, 6.6%); $\lambda_{max.}$ 277 nm (10 220); δ 1.5 (3 H, d, Me), 2.10 (2 H, m, 2′-H_2), 3.62 (2 H, m, 5′-H_2), 3.85 (1 H, m, 4′-H), 3.95 (3 H, s, OMe), 4.3 (1 H, m, 3′-H), 4.8—5.2 [3 H, m, 3′- and 5′-OH, and C*H*(SO_2Ar)], 6.20 (1 H, 2 t, 1′-H), 6.98—7.26 (2 H, m, aryl 3-H and aryl 5-H), 7.58—7.66 (2 H, m, aryl 4-H and aryl 6-H), 8.06 (1 H, s, 6-H), and 11.30 (1 H, br s, NH).

2′-*Deoxy*-5-[1-(2-*methoxyphenylsulphinyl*)*ethyl*]*uridine* (**25**).—A mixture of compound (**17**) (449 mg, 1.14 mmol) and sodium metaperiodate (243 mg, 1.14 mmol) in water (20 ml) and methanol (14 ml) was kept at 0 °C for 18 h. The solvent was removed by evaporation, and methanol (~20 ml) was added to the residue. Sodium iodate was filtered off and the filtrate was evaporated to dryness. The residue was purified by column chromatography with chloroform–methanol (6:1) as eluant. The appropriate fractions were collected, and evaporated to dryness to give the *title product* as a white solid (311 mg, 67%) (Found: C, 49.4; H, 5.5; N, 6.6. $C_{18}H_{22}N_2O_7S{\cdot}1.5H_2O$ requires C, 49.4; H, 5.8; N, 6.4%); $\lambda_{max.}$ 281 nm (9 980); δ 1.4 (3 H, m, Me), 2.1 (2 H, m, 2′-H_2), 3.55 (2 H, m, 5′-H_2), 3.8 (4 H, m, 4′-H and OMe), 4.1—4.64 [2 H, m, 3′-H and C*H*(SOAr)], 4.9 and 5.3 (2 H, 2 m, 3′- and 5′-OH), 6.18 (1 H, m, 1′-H), 6.9—7.85 (5 H, m, ArH and 6-H), and 11.1 and 11.5 (1 H, 2 br s, NH).

5-(1-*Hydroxyethyl*)-3-[(2-*methoxyethoxy*)*methyl*]-1-(*tetrahydrofuran*-2-*yl*)*uracil* (**26**).—To a solution of compound (**6**) (1.48 g, 6.7 mmol) in tetrahydrofuran (THF) (50 ml) at 0 °C was added (2-methoxyethoxy)methyl chloride (3.06 ml, 26.8 mmol). The solution was stirred at 0 °C while a solution of triethylamine (4.11 ml, 29.5 mmol) in THF (20 ml) was added dropwise during 1 h. The mixture was then stirred at ~20 °C for 18 h, and then ethanol (20 ml) was added. The solvents were then removed by evaporation to give a residual oil, which was dissolved in chloroform (100 ml) and this solution was washed with saturated aqueous sodium hydrogen carbonate (2 × 100 ml), dried, and the solvent was removed by evaporation. The residual gum was purified by column chromatography, the column being eluted with chloroform–methanol (9:1). The first fraction (~7%) was an impurity. The fractions containing the major product were collected and evaporated to dryness to give the *title product* as a glass (1 g, 50%) (Found: C, 53.7; H, 7.0; N, 8.6. $C_{14}H_{27}N_2O_6$ requires C, 53.5; H, 7.0; N, 8.9%); $\lambda_{max.}$ (EtOH and alkaline EtOH) 270 nm (9 300); δ 1.25 [3 H, d, CH(OH)*Me*], 1.8—2.4 (4 H, m, 3′- and 4′-H_2), 3.2 (3 H, s, OMe), 3.3—3.65 (4 H, m, OCH_2CH_2O), 3.7—4.2 (2 H, m, 5′-H_2), 4.5 [1 H, m, C*H*(OH)Me], 5.05 [1 H, d, CH(O*H*)Me], 5.2 (2 H, s, OCH_2N), 5.9 (1 H, dd, 2′-H), and 7.35 (1 H, s, 6-H).

3-[(2-*Methoxyethoxy*)*methyl*]-1-(*tetrahydrofuran*-2-*yl*)-5-*vinyluracil* (**27**).—To a solution of compound (**26**) (500 mg, 1.6 mmol) in DMF (5 ml) were added methanesulphonyl chloride (0.126 ml, 1.6 mmol) and *N*-methylmorpholine (0.174 ml, 1.6 mmol), and the solution was kept at 0 °C for 18 h. Ethyl acetate (100 ml) was added, and the solution was washed with saturated aqueous sodium chloride (3 × 10 ml). The organic layer was dried, and the solvent was removed by evaporation to give an oil, which was fractionated by column chromatography with toluene–acetone (3:1) as eluant. Appropriate fractions were evaporated to give, the title product as a glass (0.38 g, 80%); $\lambda_{max.}$ 238 (12 000) and 290 nm (9 000); $\lambda_{min.}$ 259 nm (4 200); δ 1.9—2.4 (4 H, m, 3′- and 4′-H_2), 3.24 (3 H, s, OMe), 3.36—3.7 (4 H, m, CH_2CH_2O), 4.4 (2 H, m, 5′-H_2), 5.09—5.24 (1 H, dd, vinylic H), 5.3 (2 H, s, OCH_2N), 5.95—6.16 (2 H, m, vinylic H and 2′-H), 6.38—6.66 (1 H, dd, vinylic H), and 7.7 (1 H, s, 6-H).

2′-*Deoxy*-3-*methyl*-5-*vinyluridine* (**29**).—To a solution of VdUrd (255 mg, 1 mmol) in 0.1M-aqueous potassium carbonate (10 ml) were added methanol (15 ml) and methyl iodide (3 ml, 48 mmol). The mixture was kept at 37 °C for 16 h, and then the solvent was removed by evaporation. The residue was purified by column chromatography, the column being eluted with chloroform–methanol (6:1). The appropriate fractions were collected, the solvent was removed by evaporation, and the residue was triturated with diethyl ether, from which white crystals of the *title product* separated (195 mg, 73%), m.p. 246—247 °C (decomp.) (Found: C, 53.8; H, 6.2; N, 10.4. $C_{12}H_{16}N_2O_5$ requires C, 53.7; H, 6.0; N, 10.4%); $\lambda_{max.}$ 237 (11 200) and 289 nm (8 250); $\lambda_{min.}$ 261 nm (4 125); δ 2.20 (2 H, m, 2′-H_2), 3.20 (3 H, s, NMe), 3.65 (2 H, m, 5′-H_2), 3.85 (1 H, m, 4′-H), 4.30 (1 H, m, 3′-H), 5.20 (3 H, m, 3′- and 5′-OH and vinylic H), 5.95 (1 H, dd, vinylic H), 6.20 (1 H, t, 1′-H), 6.50 (1 H, dd, vinylic H), and 8.25 (1 H, s, 6-H).

2′-*Deoxy*-3-*methyl*-5-[1-(2,4,5-*trichlorophenylthio*)*ethyl*]-*uridine* (**28**).—Compound (**15**) (231 mg, 0.49 mmol) and methyl iodide (5 ml, 80 mmol) were added to a mixture of 0.05M-aqueous sodium carbonate (5 ml), methanol (6 ml), and THF (20 ml), and the mixture was kept at 37 °C for 16 h. The solvents were removed by evaporation and the residue was fractionated by column chromatography. The column was eluted with chloroform–methanol (9:1), appropriate fractions were collected, and the *title product* was obtained as a white solid (130 mg, 56%) (Found: C, 44.7; H, 4.2; N, 5.9. $C_{18}H_{19}Cl_3N_2O_5S$ requires C, 44.9; H, 4.0; N, 5.9%); $\lambda_{max.}$ 267 nm (14 810); δ 1.55 (3 H, d, Me), 2.20 (2 H, m, 2′-H_2), 3.20 (3 H, s, NMe), 3.60 (2 H, m, 5′-H_2), 3.85 (1 H, m, 4′-H), 4.25 (1 H, m, 3′-H), 4.60 [1 H, q, C*H*(SAr)], 5.10 (1 H, t, 5′-OH), 5.25 (1 H, d, 3′-OH), 6.20 (1 H, 2 t, 1′-H), 7.73 and 7.70 (2 H, 2 s, ArH), and 8.08 (1 H, s, 6-H).

The Action of Bases on 2′-*Deoxy*-5-[(1-*substituted*)*ethyl*]-*uridines*.—(*a*) Compound (2 mg) was dissolved in dry DMF (2

ml), potassium t-butoxide (1 mol equiv.) was added, and the solution was kept at 37 °C for 3 days (or at 90 °C where indicated). Samples were removed and applied as a band to t.l.c. silica gel plates, which were run in chloroform–methanol (9:1). Markers of VdUrd and 2′-deoxy-5-(1-hydroxy)ethyluridine (**4**; X = OH) were used. The areas with the same R_F value as VdUrd were eluted with ethanol and the u.v. absorption spectra were measured. In all cases these corresponded with the spectrum of VdUrd and the extinction gave an approximate measure of the amount of VdUrd produced. The results are as given in the Discussion section.

(*b*) The compound (2 mg) was dissolved in (i) 0.1M-aqueous NaOH (2 ml) or (ii) 0.1M-phosphate buffer, pH 7.6 (2 ml), and examined as in (*a*). The results are given in the Discussion section.

Biological Evaluation

Antiviral Activity Assays.—These were based upon the inhibition of virus-induced cytopathogenicity in PRK cells, with herpes simplex type 1 (HSV-1), herpes simples virus type 2 (HSV-2), vaccinia virus (VV), or vesicular stomatitis virus (VXV) as the challenge virus. Further details of the procedure are described in ref. 2.

Antitumour Cell Activity Assays.—These were based upon the inhibitory activity of the compounds on the proliferation of murine leukaemia L1210 cells according to the procedure described in ref. 3.

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