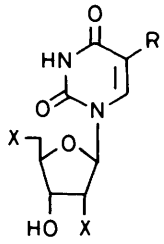
Nucleosides. Part 6.[1] New Chemical Modification of the Ribosyl Moiety in Uridines; Synthesis of 2,2'-Anhydro-1-[5-deoxy-5-(substituted thio)-β-D-arabinofuranosyl]uracil Derivatives and Their Conversion into 3',5'-Epithiopyrimidine Nucleosides[2]

Kosaku Hirota,* Yukio Kitade, Tetsuo Tomishi, and Yoshifumi Maki
Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502, Japan
Erik De Clercq
Rega Institute for Medical Research, University of Leuven, B-3000, Leuven, Belgium

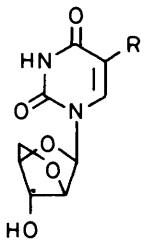
Treatment of 5-substituted 2',5'-dichloro-2',5'-dideoxyuridines (**1**) with thiols such as thiophenol, thioacetic *S*-acid, thiobenzoic *S*-acid, toluene-α-thiol, and ethanethiol in the presence of triethylamine or 1,1,3,3-tetramethylguanidine in *N*,*N*-dimethylformamide (DMF) gave the corresponding 2,2'-anhydro-1-[5-deoxy-5-(substituted thio)-β-D-arabinofuranosyl]uracils (**2a—f**) in good yield. Treatment of 5-substituted 2,2'-anhydro-1-(5-acetylthio-5-deoxy-β-D-arabinofuranosyl)uracils (**2b**) and (**2f**), prepared with ease by the reaction of (**1**) with thioacetic *S*-acid, with methanolic sodium methoxide gave the corresponding 1-(3,5-dideoxy-3,5-epithio-β-D-xylofuranosyl)uracils (**9a**) and (**9c**) fused with a thietane ring in the sugar moiety. None of the newly synthesized nucleosides displayed appreciable cytotoxicity or antiviral activity in primary rabbit cell cultures.

Recent articles from our laboratory have described a convenient method for the synthesis of 2',5'-dideoxy-2',5'-dihalogenouridines (**I**) upon treatment of uridine derivatives with the Vilsmeier-Haack reagent[3] and the versatile utility of (**I**) for the chemical modification of uridine derivatives, involving its conversions into biologically interesting 1-(2,5-anhydro-β-D-arabinofuranosyl)uracil derivatives (**II**)[4] and 2-*N*-substituted 1-β-D-arabinofuranosylisocytosine derivatives (**III**).[5]

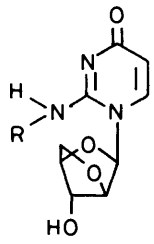
In continuation of our investigation on the reactivity of 2',5'-dichlorouridines (**1**) towards various nucleophiles, we found a simple procedure for the preparation of 2,2'-anhydro-1-[5-deoxy-5-(substituted thio)-β-D-arabinofuranosyl]uracils (**2a—f**) by employment of thiols as nucleophiles. The present paper describes the above result and conversion of 2,2'-anhydro-5'-acetylthiouridines (**2b**) and (**2f**) into novel 1-(3,5-dideoxy-3,5-epithio-β-D-xylofuranosyl)uracils (**9a**) and (**9c**), which possess a thietane ring in the sugar moiety. Isolation of nucleosides fused with a thietane ring[6] in the sugar moiety is unprecedented, although the formation of this type of compound has been proposed as a transient reaction intermediate.[7] The present findings provide a new methodology for the chemical modification of uridine derivatives.



(I)



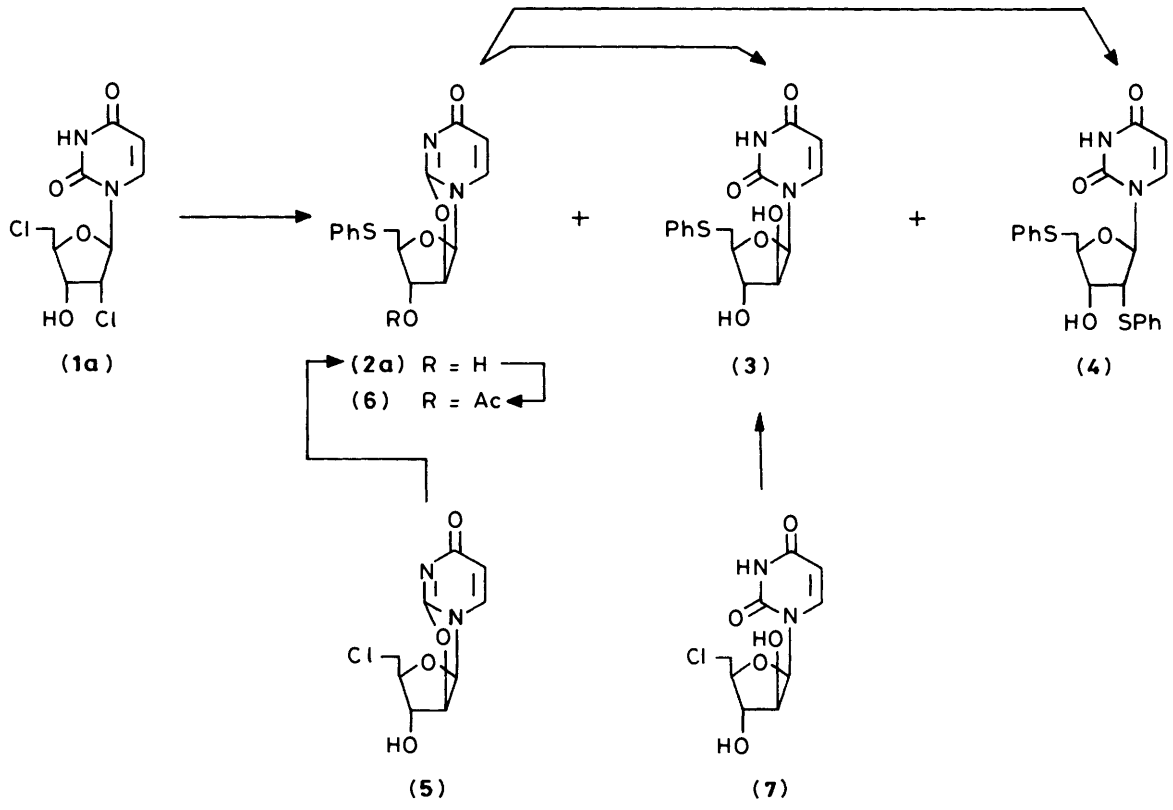
(II)



(III)

Refluxing of 2',5'-dichloro-2',5'-dideoxyuridine (**1a**)[3] with thiophenol (3.0 equiv.) and sodium methoxide (2.5 equiv.) in methanol under a nitrogen atmosphere for 72 h gave 2,2'-anhydro-1-(5-deoxy-5-phenylthio-β-D-arabinofuranosyl)uracil (**2a**), 1-(5-deoxy-5-phenylthio-β-D-arabinofuranosyl)uracil (**3**), and 2',5'-dideoxy-2',5'-diphenylthiouridine (**4**) in 39, 8, and 21% yields, respectively. Use of triethylamine instead of sodium methoxide as a base, gave exclusive formation of compound (**2a**). Thus, the 2,2'-anhydrouridine (**2a**) was obtained in 74% yield upon treatment of the dichlorouridine (**1a**) with thiophenol (1 equiv.) in the presence of triethylamine in *N*,*N*-dimethylformamide (DMF) under nitrogen atmosphere at 100 °C for 4 h. The other products (**3**) and (**4**) were not detected in the reaction mixture by means of t.l.c. The structure of (**2a**) was totally supported by microanalytical results and spectral data. In the ^{1}H n.m.r. spectrum of (**2a**), the distinct upfield shift (0.6—0.9 p.p.m.) of the 5'-proton signals compared with those of the 5'-unsubstituted uridine derivative clearly indicated the presence of the sulphur function at the 5'-position. The structure of (**2a**) was confirmed by comparison with a specimen prepared alternatively by the reaction of 2,2'-anhydro-1-(5-chloro-5-deoxy-β-D-arabinofuranosyl)uracil (**5**)[3] with thiophenol in the presence of triethylamine in DMF. Acetylation of (**2a**) with acetic anhydride in dry pyridine gave the corresponding 3'-*O*-acetyl derivative (**6**). Hydrolysis of (**2a**) with aqueous sodium hydroxide resulted in the formation of 5'-phenylthioarabinofuranosyl derivative (**3**) in 92% yield. Compound (**3**) was obtained in 55% yield upon treatment of 1-(5-chloro-5-deoxy-β-D-arabinofuranosyl)uracil (**7**)[8] with thiophenol and triethylamine in DMF. Further treatment of (**2a**) with thiophenol gave 2',5'-dithiophenyluridine (**4**) in 87% yield. Analogous cleavage of the 2,2'-anhydro bond by action of thiophenol has been observed in the conversion of 2,2'-anhydro-1-β-D-arabinofuranosyluracil into 2'-deoxy-2'-phenylthiouridine.[9]

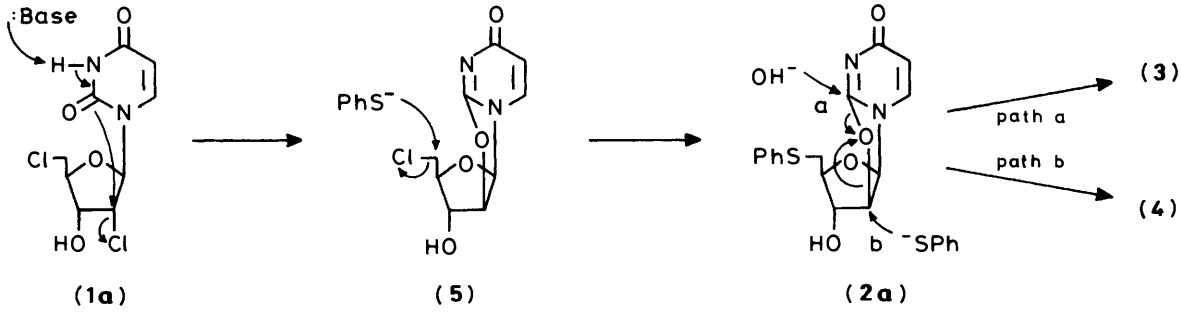
On the basis of the above results, a reaction sequence for the formation of (**2a**), (**3**), and (**4**) from the 2',5'-dichlorouridine (**1a**) is outlined as shown in Scheme 2. The base-catalysed cyclisation of (**1a**) gives the 2,2'-anhydro intermediate (**5**), which is converted into (**2a**) by nucleophilic attack of thiophenolate ion at the 5'-position of (**5**). The compound (**2a**) could undergo hydrolysis of the 2,2'-bond by hydroxide ion derived from water contained in the solvent to give the arabinofuranosyl derivative (**3**) (path a). Nucleophilic attack of another molecule of thiophenolate ion at the 2'-position of (**2a**) leads to the formation of (**4**) (path b). Difference of the reaction sites between hydroxide and thiophenolate ions can be rationalised on the basis of the hard and soft acids and bases (HSAB) principle.[10] The 2-position of the pyrimidine ring and the 2'-



Scheme 1.

position of the ribosyl moiety in the 2,2′-anhydrouridine (**2a**) are regarded as hard and soft sites, respectively, and a soft thiolate anion attacks the 2′-position, whereas hard hydroxide ion causes substitution at the 2-position.

The reaction of (**1a**) with ethanethiol in the presence of 1,1,3,3-tetramethylguanidine gave the corresponding product (**2e**) together with 2′,5′-dideoxy-2′,5′-diethylthiouridine (**8**). 2′,5′-Dichloro-2′,5′-dideoxy-5-fluorouridine (**1b**) was allowed to



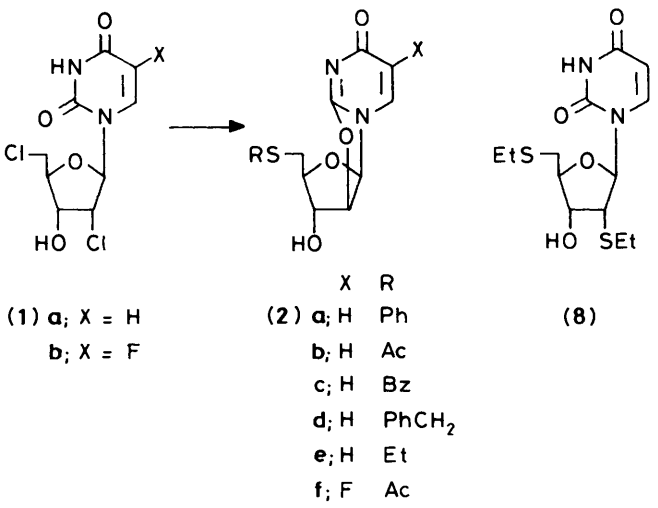
Scheme 2.

Analogous treatment of (**1a**) with thioacetic *S*-acid and thiobenzoic *S*-acid in the presence of triethylamine afforded the corresponding 2,2′-anhydro-1-[5-deoxy-5-(substituted thio)-β-D-arabinofuranosyl]uracils (**2b**) and (**2c**) in 66 and 55% yields, respectively. In the reaction of (**1a**) with toluene-α-thiolate ion under similar conditions, none of the expected 5′-benzylthio derivative (**2d**) was formed, the 2,2′-anhydrouridine (**5**) being detected as the sole product by t.l.c. analysis of the reaction mixture. Employment of more basic 1,1,3,3-tetramethylguanidine instead of triethylamine, however, led to the formation of product (**2d**) in accordance with our expectation. react with thioacetic *S*-acid to produce smoothly 1-(5-acetyl thio-5-deoxy-β-D-arabinofuranosyl)-2,2′-anhydro-5-fluorouracil (**2f**) in 92% yield.

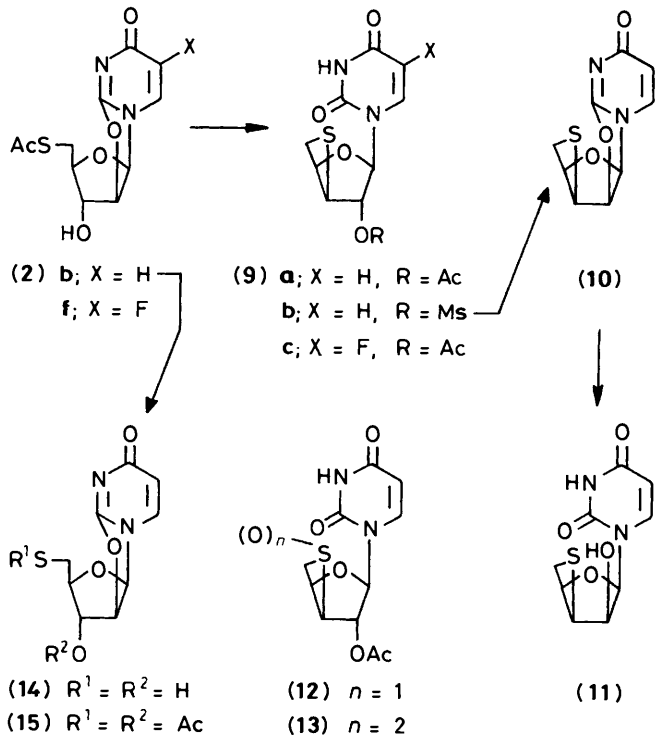
The 5′-acetylthio-2,2′-anhydrouridine (**2b**) was refluxed in methanolic sodium methoxide for 1 h and the resulting clear solution was neutralised with Amberlite CG-50 (H^+). After removal of the solvent, acetylation of the residue with acetic anhydride in pyridine allowed isolation of 1-(2-*O*-acetyl-3,5-dideoxy-3,5-epithio-β-D-xylofuranosyl)uracil (**9a**) in 67% yield. An attempt to isolate the nonacetylated compound corresponding to (**9a**) in a pure state was unsuccessful. The structure of (**9a**)

Table. ^{1}H N.m.r. analysis of the furanose ring protons on the 3′,5′-epithio and 3′,5′-epidithio pyrimidine nucleosides

Compound no.	1′-H	2′-H	3′-H	4′-H	5′-H	5′-H
(**9a**)	6.31 (d)	5.28—5.16	4.03 (dd)	5.28—5.16	3.58 (dd)	2.90 (dd)
	J 3.7 Hz		*J* 5.6, 1.0 Hz		*J* 11.0, 4.9 Hz	*J* 11.0, 0.8 Hz
(**9b**)	6.14 (d)	5.48 (dd)	4.29 (dd)	5.31 (dt)	3.58 (dd)	3.04 (dd)
	J 3.0 Hz	*J* 3.0, 1.5 Hz	*J* 5.7, 1.5 Hz	*J* 5.2, 1.5 Hz	*J* 10.2, 5.4 Hz	*J* 10.2, 1.0 Hz
(**9c**)	6.31 (dd)	5.40—5.13	4.08 (dd)	5.40—5.13	3.62 (dd)	2.92 (dd)
	J 3.5, 1.5 Hz		*J* 6.0, 1.2 Hz		*J* 11.3, 6.3 Hz	*J* 11.3, 0.8 Hz
(**10**)	6.40 (d)	5.56 (dd)	4.46 (dd)	5.24	3.44 (dd)	2.61 (dd)
	J 5.9 Hz	*J* 7.6, 5.9 Hz	*J* 7.6, 6.6 Hz		*J* 11.0, 6.1 Hz	*J* 11.0, 3.0 Hz
(**11**)	6.14 (d)	4.70—4.10		4.88 (dt)	3.50 (dd)	2.83 (dd)
	J 5.1 Hz			*J* 5.9, 1.7 Hz	*J* 10.4, 5.3 Hz	*J* 10.4, 2.3 Hz
(**13**)	6.25 (d)	5.46 (dd)	5.03 (t)	5.32—5.23	4.60 (dd)	4.25 (d)
	J 6.4 Hz	*J* 6.1, 2.4 Hz	*J* 5.4 Hz		*J* 14.7, 1.5 Hz	*J* 14.7 Hz
(**16b**)	5.97 (d)	5.06 (t)	4.42 (t)	5.27 (dd)	3.56 (d)	2.99 (dd)
	J 6.6 Hz	*J* 6.1 Hz	*J* 6.1 Hz	*J* 6.6, 3.7 Hz	*J* 13.2 Hz	*J* 13.2, 3.9 Hz



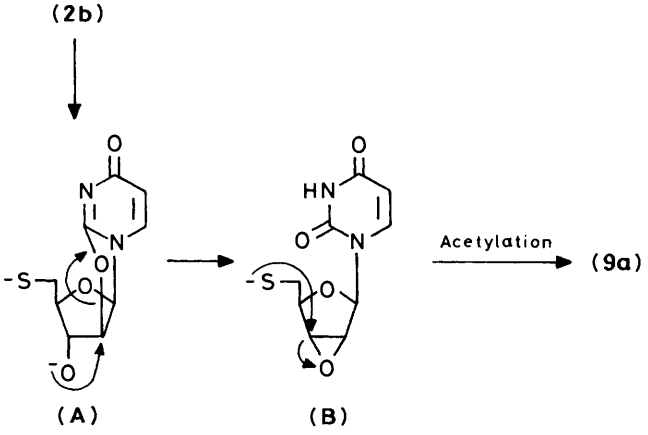
Scheme 3.



Scheme 4.

was deduced from its spectral (i.r., ^{1}H n.m.r., u.v., and mass) data (see Experimental section and Table) and a consideration of the reaction sequence described below.

A plausible reaction sequence for the formation of (**9a**) is outlined in Scheme 5. Deacylation of the 5′-acetylthio group and deprotonation of the 3′-hydroxy group by base result in the formation of a dianion (**A**). The subsequent formation of an epoxide intermediate (**B**) could occur *via* attack of the 3′-*O* anionic site at the 2′-position and concurrent cleavage of the 2,2′-anhydro bond. Fission of the epoxide ring by the attack of 5′-thiolate ion at the 3′-position could produce the 3′,5′-epithio derivative (**9a**). This reaction sequence for the formation of (**9a**) formally parallels that proposed previously for the formation of 1-(3-deoxy-3-ethylthio-β-D-xylofuranosyl)uracil in the reaction of 2,2′-anhydro-1-β-D-arabinofuranosyluracil with ethanethiolate ion.[11] The above considerations cannot rule out an alternative structure for (**9a**), 1-(3-*O*-acetyl-2,5-dideoxy-2,5-epithio-β-D-arabinofuranosyl)uracil involving the 2′,5′-sulphur linkage. Conclusive structural proof of (**9a**) was obtained on the basis of following experimental facts. Treatment of (**2b**) with sodium methoxide followed by the reaction with methanesulphonyl chloride instead of acetic anhydride in the above reaction afforded the corresponding 2′-*O*-mesyl derivative (**9b**) in 72% yield. Compound (**9b**) was smoothly converted upon treatment with sodium methoxide (1 equiv.) in methanol under



Scheme 5.

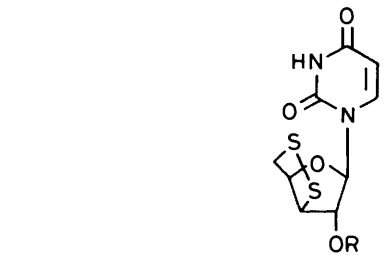
reflux for 30 min into 2,2′-anhydro-1-(3,5-dideoxy-3,5-epithio-β-D-lyxofuranosyl)uracil (**10**) quantitatively. This result clearly indicates that compound (**9a**) has the 3′,5′-epithio structure rather than the alternative 2′,5′-epithio structure, formation of the 2,3′-anhydro bond in the latter structure being greatly constrained by severe steric hindrance. Hydrolysis of (**10**) with sodium hydroxide at room temperature for 1.5 h led to the formation of 1-(3,5-dideoxy-3,5-epithio-β-D-lyxofuranosyl)-uracil (**11**) in 65% yield. The structural change in the transformation [(**9b**) ⟶ (**10**) ⟶ (**11**)] is consistent with the change of coupling constant ($J_{1',2'}$) between an anomeric proton (1′-H) and a 2′-proton (2′-H) in their ^{1}H n.m.r. spectra (see Table): the coupling constants ($J_{1',2'}$ 5.1—5.9 Hz) of (**10**) and (**11**) are larger than those ($J_{1',2'}$ 3.0—3.7 Hz) of (**9a—c**) which possess a β-proton at the 2′-position.

The 5-fluoro derivative (**2f**) was also converted into the corresponding 3′,5′-epithio-5-fluoro derivative (**9c**) in 80% yield upon treatment with methanolic sodium methoxide.

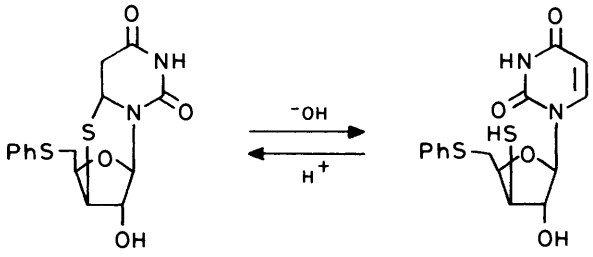
Oxidation of (**9a**) with *m*-chloroperbenzoic acid (MCPBA) (1 equiv.) gave the corresponding sulphoxide (**12**), which was shown to be a mixture of two isomeric sulphoxides by ^{1}H n.m.r. spectral analysis. Further oxidation of (**12**) with MCPBA or oxidation of (**9a**) with an excess of MCPBA gave the corresponding sulphone (**13**). The oxidation of (**9a**) into the sulphone (**13**) caused a large downfield ^{1}H n.m.r. shift of 3′-H and 5′-H (see Table), which also supports the 3′,5′-epithio structure of (**9a**).

Treatment of (**2b**) with triethylamine in methanol gave 5′-thiol derivative (**14**). Acetylation of (**14**) and (**2b**) led to formation of the same diacetyl derivative (**15**).

The 2,2′-anhydro-5′-acetylthio derivative (**2b**) reacted with sodium disulphide (3 equiv.) in ethanol under reflux, to give 1-(3,5-dideoxy-3,5-epidithio-β-D-xylofuranosyl)uracil (**16a**) in 39% yield. Acetylation of (**16a**) with acetic anhydride–pyridine gave the corresponding acetate (**16b**). An alternative synthesis of (**16a**) involved reaction of the 2′,5′-dichlorouridine (**1a**) with sodium disulphide. The u.v. absorption spectrum of (**16a**) and



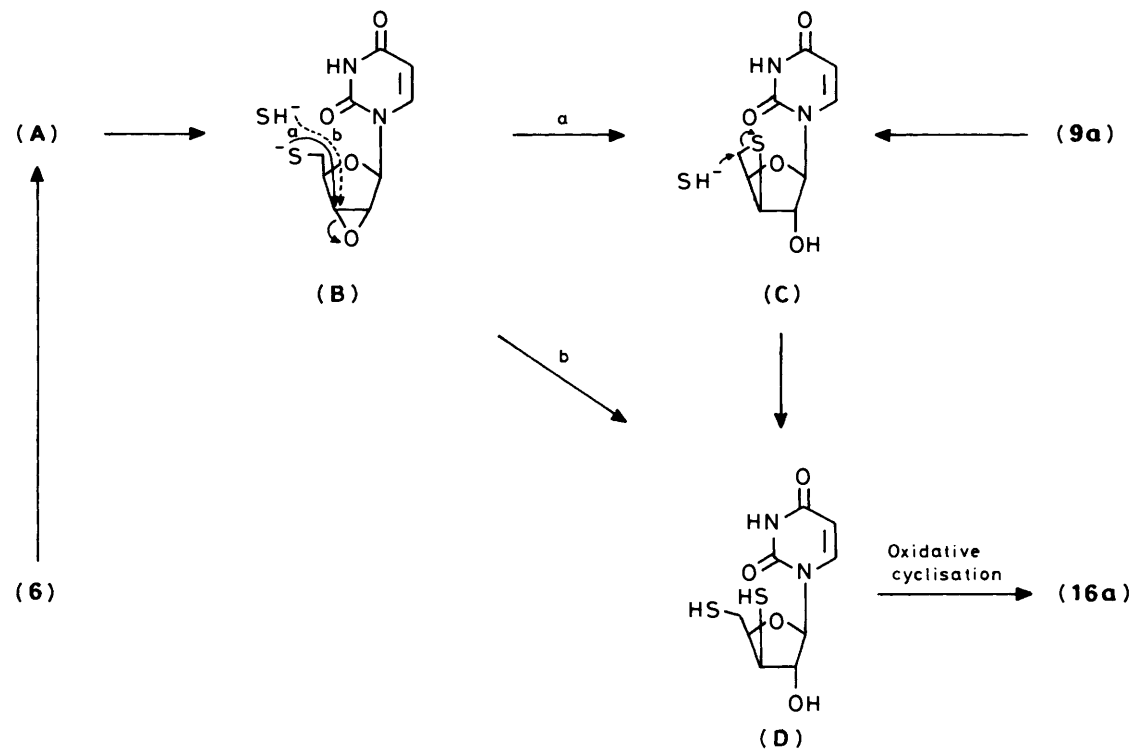
(**16**) a; R = H
b; R = Ac



(**17**) (**18**)

(**16b**) is superimposable on that of uridine. These facts fully support structure (**16**). A thymidine analogue of (**16a**) has been prepared by reaction of 2,5′-anhydro-3′-*O*-mesylthymidine or 3′,5′-di-*O*-mesylthymidine with hydrogen sulphide.[7] Insight into the mechanisms for these reactions was achieved by reaction of the thietane (**9a**) with sodium disulphide under conditions similar to those used for (**2b**); the 3′,5′-epidithio derivative (**16a**) was formed in only 17% yield.

Taking into consideration the above facts, reaction sequences for the formation of (**16a**) from (**1a**), (**2b**), and (**9a**) are outlined in Scheme 6. A key intermediate epoxide (**B**) could be formed *via*



Scheme 6.

(**A**) from (**2b**) and (**1a**) (see Scheme 5). Two reaction paths (a and b) can be considered for formation of the dithiol intermediate (**D**): path a involves ring-cleavage of the thietane intermediate (**C**) by attack of thiolate ion (SH^-) at the 5′-position and path b involves direct attack of SH^- at the 3′-position of the epoxide (**B**). The dithiol (**D**) produced *via* path a or b could undergo an oxidative cyclisation to give the epidithio derivative (**16a**). Since compounds (**16a**) from (**9a**) were formed only in low yield it is, at present, hard to choose between path a and path b for the reaction process.

Treatment of (**9a**) with sodium thiophenolate in ethanol under reflux for 24 h resulted in formation of 6,3′-epithio-5,6-dihydro-1-(3,5-dideoxy-5-phenylthio-β-D-xylofuranosyl)uracil (**17**) in 29% yield. The absence of u.v. absorption characteristics of the uracil ring (258 nm) strongly supports the 6,3′-epithio-5,6-dihydro structure (**17**). The u.v. spectrum of compound (**17**) changed to that of the uracil derivatives upon addition of sodium hydroxide and showed a 5′-phenylthiouridine-like absorption; this indicated occurrence of 6,3′-epithio bond cleavage leading to 1-(3,5-dideoxy-3-mercapto-5-phenylthio-β-D-xylofuranosyl)uracil (**18**). Facile neighbouring group participation of the 5′-thiol grouping to the uracil ring is precedented.[12,13] The reaction sequence for the formation of (**17**) from (**9a**) can be considered as follows: cleavage of the C(5′)–S bond by attack of thiophenolate ion at the 5′-position and subsequent intramolecular addition of 3′-thiolate ion on the 6-position of the uracil ring gives the adduct (**17**).

Compounds (**2a**—**f**), (**3**), (**9a**), and (**11**)—(**15**) were evaluated for cytotoxicity and antiviral activity in primary rabbit kidney cell cultures. None of these compounds showed appreciable cytotoxicity and antiviral activity against herpes simplex virus-1 (strain KOS), herpes simplex virus-2 (strain G), vaccinia virus, and vesicular stomatitis virus when bioassayed using tubercidin, (*S*)-DHPA [(*S*)-9-(2,3-dihydroxypropyl)adenine], ribavirin, and carbocyclic 3-deaza-adenosine as reference compounds.[14]

Experimental

M.p.s were determined on a Yanagimoto melting-point apparatus and are uncorrected. ^{1}H N.m.r. spectra were determined with a Hitachi-Perkin-Elmer R-20B 60 MHz instrument and a JEOL JNM-GX270 NMR Spectrometer, using tetramethylsilane in $CDCl_3$ or sodium 2,2-dimethyl-2-silapentane-5-sulphonate in $(CD_3)_2SO$ as internal standards. Chemical shifts are reported in p.p.m. (δ) and *J* values in Hz. ^{13}C N.m.r. spectra were determined with a JEOL JNM-FX100 Fourier transform spectrometer operating at 25.00 MHz, with tetramethylsilane as internal standard. U.v. spectra were recorded on a Shimazu 323 Spectrophotometer. Mass spectra were taken on a JEOL JMS-D300 machine operating at 70 eV. Elemental analyses were carried out at the Microanalytical Laboratory of our University. Column chromatography was carried out on silica gel (Wako gel C-300).

Reaction of 2′,5′-Dichloro-2′,5′-dideoxyuridine (**1a**) *with Sodium Thiophenolate.*—A solution of 2′,5′-dichloro-2′,5′-dideoxyuridine (**1a**)[3] (500 mg, 1.7 mmol) and thiophenol (561 mg, 5.7 mmol) in methanolic sodium methoxide [prepared from Na (100 mg, 4.3 mmol) in absolute methanol (100 ml)] was refluxed for 72 h under an N_2 atmosphere. The solvent was neutralised with Amberlite CG-50 (H^+) and the exchanger was washed with water. The combined solvents were removed under reduced pressure and the residue was chromatographed on a silica gel column eluting with chloroform–methanol (50:1). The first fraction was evaporated and the residue was recrystallised from methanol to give *2′,5′-dideoxy-2′,5′-diphenylthiouridine* (**4**) (160 mg, 21%), m.p. 130 °C (Found: C, 57.05; H, 5.25; N, 6.2. $C_{21}H_{20}N_2O_4S_2$·CH_3OH requires C, 57.37; H, 5.25; N, 6.08%); $\lambda_{max.}$(EtOH) 254 nm (log ε 4.30); *m/z* 429 ($M^+ + 1$); δ_H[$(CD_3)_2SO$] 11.16 (1 H, br s, HN[3]), 7.60—7.10 (11 H, m, S-Ph and 6-H), 6.40—6.00 (2 H, br, 1′-H and OH), 5.46 (1 H, d, *J* 8.3 Hz, 5-H), 4.60—3.80 (4 H, m, 2′-, 3′-, and 4′-H and CH_3OH), 3.50—3.10 (5 H, br, 5′-H and CH_3OH).

The second fraction was evaporated and the residue was recrystallised from water to give 1-(*5-deoxy-5-phenylthio-β-D-arabinofuranosyl)uracil* (**3**) (50 mg, 8%), m.p. 232 °C (Found: C, 53.75; H, 4.7; N, 8.3. $C_{15}H_{16}N_2O_5S$ requires C, 53.56; H, 4.79; N, 8.33%); $\lambda_{max.}$(EtOH) 255 nm (log ε 4.24); *m/z* 336 (M^+); δ_H[$(CD_3)_2SO$] 11.26 (1 H, br, HN[3]), 7.58—7.15 (6 H, m, S-Ph and 6-H), 6.05 (1 H, d, *J* 3.3 Hz, 1′-H), 5.90—5.45 (3 H, m, 5-H, 3′- and 2′-OH), 4.10—3.70 (3 H, br, 2′-, 3′-, and 4′-H), and 3.50—3.15 (2 H, br, 5′-H).

The third fraction was evaporated and the residue was recrystallised from water to give *2,2′-anhydro-1-(5-deoxy-5-phenylthio-β-D-arabinofuranosyl)uracil* (**2a**) (220 mg, 39%), m.p. 195 °C (Found: C, 56.4; H, 4.5; N, 8.75. $C_{15}H_{14}N_2O_4S$ requires C, 56.59; H, 4.43; N, 8.80%); $\lambda_{max.}$(EtOH) 215sh (log ε 4.16) and 251 nm (4.14); *m/z* 318 (M^+); δ_H[$(CD_3)_2SO$] 7.89 (1 H, d, *J* 7.5 Hz, 6-H), 7.30 (5 H, br s, S-Ph), 6.36 (1 H, d, *J* 5.3 Hz, 1′-H), 6.09 (1 H, d, *J* 4.5 Hz, OH), 5.89 (1 H, d, *J* 7.5 Hz, 5-H), 5.28 (1 H, br d, *J* 5.3 Hz, 2′-H), 4.50—4.00 (2 H, br, 3′- and 4′-H), and 3.10—2.80 (2 H, m, 5′-H).

2,2′-Anhydro-1-(5-deoxy-5-phenylthio-β-D-arabinofuranosyl)-uracil (**2a**).—A solution of 2′,5′-dichloro-2′,5′-dideoxyuridine (**1a**) (500 mg, 1.8 mmol), thiophenol (200 mg, 1.8 mmol), and triethylamine (900 mg, 8.9 mmol) in DMF (30 ml) was heated at 100 °C for 4 h under an N_2 atmosphere. The mixture was evaporated under reduced pressure and the residue was treated with water. The resulting precipitate was filtered off and recrystallised from water to give compound (**2a**) (419 mg, 74%), which was identical with the product prepared above.

Preparation of (**2a**) *by Reaction of 2,2′-Anhydro-1-(5-chloro-5-deoxy-β-D-arabinofuranosyl)uracil* (**5**) *with Thiophenol.*—A solution of 2,2′-anhydro-1-(5-chloro-5-deoxy-β-D-arabinofuranosyl)uracil (**5**)[3] (244 mg, 1.0 mmol), thiophenol (110 mg, 1.0 mmol), and triethylamine (500 mg, 5.0 mmol) in DMF (30 ml) was heated at 100 °C for 3 h under an N_2 atmosphere. The mixture was evaporated under reduced pressure and the residue was treated with water. The resulting precipitate was filtered off and recrystallised from water to give (**2a**) (200 mg, 63%) which was identical with the product prepared above.

1-(*5-Deoxy-5-phenylthio-β-D-arabinofuranosyl)uracil* (**3**).—Compound (**2a**) (100 mg, 0.31 mmol) was added to a solution of sodium hydroxide (15 mg, 0.38 mmol) in water (20 ml), and the suspension was stirred for 8 h at room temperature. The resulting precipitate was filtered off and the filtrate neutralised with Amberlite GC-50 (H^+) and evaporated under reduced pressure. The combined precipitate and the residue were recrystallised from water to afford (**3**) (97 mg, 92%), which was identical with the product prepared above.

2′,5′-Dideoxy-2′,5′-diphenylthiouridine (**4**).—A solution of compound (**2a**) (318 mg, 1.0 mmol), thiophenol (200 mg, 1.8 mmol), and triethylamime (500 mg, 5.0 mmol) in DMF (30 ml) was heated at 100 °C for 24 h under an N_2 atmosphere. The mixture was evaporated under reduced pressure and the residue was twice crystallised from methanol. It gave compound (**4**) (400 mg, 87%), which was identical with the product prepared above.

1-(3-O-*Acetyl-5-deoxy-5-phenylthio-β-D-arabinofuranosyl)-2,2′-anhydrouracil* (**6**).—A solution of compound (**2a**) (500 mg, 1.6 mmol) in pyridine (5 ml) and acetic anhydride (5 ml) was

stirred for 1 h at room temperature and the solution was poured into ice–water (10 ml). The resulting precipitate was filtered off and recrystallised from ethanol to give compound (**6**) (335 mg, 60%), m.p. 197—198 °C (Found: C, 56.6; H, 4.45; N, 7.8. $C_{17}H_{16}N_2O_5S$ requires C, 56.66; H, 4.48; N, 7.77%); $\lambda_{max.}$(EtOH) 215sh (log ε 4.14) and 250 nm (4.13); *m/z* 360 (M^+); δ_H[$(CD_3)_2SO$] 7.91 (1 H, d, *J* 7.4 Hz, 6-H), 7.31 (5 H, s, S-Ph), 6.43 (1 H, d, *J* 6.0 Hz, 1′-H), 5.90 (1 H, d, *J* 7.4 Hz, 5-H), 5.54 (1 H, dd, *J* 6.0 and 0.8 Hz, 2′-H), 5.38 (1 H, dd, *J* 1.8 and 0.8 Hz, 3′-H), 4.43 (1 H, m, 4′-H), 3.06 (2 H, m, 5′-H), and 2.10 (3 H, s, $COCH_3$).

1-(5-*Acetylthio*-5-*deoxy*-β-D-*arabinofuranosyl*)-2,2′-*anhydrouracil* (**2b**).—A mixture of compound (**1a**)[3] (300 mg, 1.1 mmol), thioacetic *S*-acid (100 mg, 1.3 mmol), and triethylamine (540 mg, 5.3 mmol) in DMF (30 ml) was heated at 100 °C for 4 h under an N_2 atmosphere. The mixture was evaporated under reduced pressure and the residue was chromatographed on a silica gel column eluting with chloroform–methanol (50:1). Recrystallisation from ethanol gave compound (**2b**) (200 mg, 66%), m.p. 198—199 °C (Found: C, 46.65; H, 4.3; N, 9.85. $C_{11}H_{12}N_2O_5S$ requires C, 46.47; H, 4.25; N, 9.85%); $\lambda_{max.}$(EtOH) 226 (log ε 4.15) and 245nm (3.96); *m/z* 284 (M^+); δ_H[$(CD_3)_2SO$] 7.91 (1 H, d, *J* 7.5 Hz, 6-H), 6.36 (1 H, d, *J* 5.6 Hz, 1′-H), 6.11 (1 H, br d, *J* 3.8 Hz, OH), 5.92 (1 H, d, *J* 7.5 Hz, 5-H), 5.28 (1 H, dd, *J* 5.6 and 0.8 Hz, 2′-H), 4.50—4.00 (2 H, br, 3′- and 4′-H), 3.25—2.70 (2 H, m, 5′-H), and 2.32 (3 H, s, $COCH_3$).

2,2′-*Anhydro*-1-(5-*benzoylthio*-5-*deoxy*-β-D-*arabinofuranosyl*)*uracil* (**2c**).—A solution of compound (**1a**) (500 mg, 1.8 mmol), thiobenzoic *S*-acid (250 mg, 1.8 mmol), and triethylamine (900 mg, 8.9 mmol) in DMF (30 ml) was heated at 100 °C for 4 h under an N_2 atmosphere. The mixture was evaporated under reduced pressure and the residue was chromatographed on a silica gel column eluting with chloroform–methanol (50:1). Recrystallisation of the product from water gave compound (**2c**) (340 mg, 55%), m.p. 203 °C (Found: C, 55.65; H, 4.1; N, 8.15. $C_{16}H_{14}N_2O_5S$ requires C, 55.48; H, 4.07; N, 8.09%); $\lambda_{max.}$(EtOH) 238 (log ε 4.26) and 256sh nm (4.12); *m/z* 345 ($M^+ - 1$); δ_H[$(CD_3)_2SO$] 8.15—7.50 (6 H, m, COC_6H_5 and 6-H), 6.38 (1 H, d, *J* 5.9 Hz, 1′-H), 6.15 (1 H, d, *J* 4.4 Hz, OH), 5.88 (1 H, d, *J* 7.2 Hz, 5-H), 5.30 (1 H, br d, *J* 5.9 Hz, 2′-H), 4.55—4.00 (2 H, m, 3′- and 4′-H), and 3.30—2.98 (2 H, m, 5′-H).

2,2′-*Anhydro*-1-(5-*benzylthio*-5-*deoxy*-β-D-*arabinofuranosyl*)-*uracil* (**2d**).—A solution of compound (**1a**) (281 mg, 1 mmol), toluene-α-thiol (124 mg, 1.0 mmol) and 1,1,3,3-tetramethylguanidine (575 mg, 5.0 mmol) in DMF (30 ml) was heated at 100 °C for 3 days in a sealed tube. The mixture was evaporated under reduced pressure and the residue was chromatographed on a silica gel column eluting with chloroform–methanol (50:1). Recrystallisation of the product from water gave compound (**2d**) (140 mg, 42%), m.p. 169 °C (Found: C, 57.55; H, 4.75; N, 8.35. $C_{16}H_{16}N_2O_4S$ requires C, 57.82; H, 4.85; N, 8.43%); $\lambda_{max.}$(EtOH) 215sh (log ε 4.15) and 245 (3.90); *m/z* 332 (M^+); δ_H[$(CD_3)_2SO$] 7.95 (1 H, d, *J* 7.5 Hz, 6-H), 7.29 (5 H, s, Ph), 6.37 (1 H, d, *J* 5.3 Hz, 1′-H), 6.08 (1 H, br d, *J* 4.5 Hz, OH), 5.94 (1 H, d, *J* 7.5 Hz, 5-H), 5.29 (1 H, dd, *J* 5.3 and 0.8 Hz, 2′-H), 4.50—4.05 (2 H, m, 3′- and 4′-H), 3.78 (2 H, s, CH_2Ph), and 2.45 (2 H, br, 5′-H).

2,2′-*Anhydro*-1-(5-*deoxy*-5-*ethylthio*-β-D-*arabinofuranosyl*)-*uracil* (**2e**) *and* 2′,5′-*Dideoxy*-2′,5′-*diethylthiouridine* (**8**).—A mixture of compound (**1a**) (281 mg, 1.0 mmol), ethanethiol (62 mg, 1.0 mmol), and 1,1,3,3-tetramethylguanidine (575 mg, 5.0 mmol) was heated at 100 °C for 2 days in a sealed tube. The mixture was evaporated under reduced pressure and the residue was chromatographed on a silica gel column eluting with chloroform–methanol (50:1). The faster moving fraction was evaporated and the residue was recrystallised from water to give compound (**8**) (100 mg, 30%), m.p. 149—150 °C (Found: C, 46.85; H, 6.15; N, 8.45. $C_{13}H_{20}N_2O_4S_2$ requires C, 46.97; H, 6.06; N, 8.43%); $\lambda_{max.}$(EtOH) 261 nm (log ε 3.99); *m/z* 332 (M^+); δ_H[$(CD_3)_2SO$] 11.38 (1 H, br s, HN^3), 7.76 (1 H, d, *J* 8.3 Hz, 6-H), 6.03 (1 H, d, *J* 9.0 Hz, 1′-H), 5.90—5.60 (2 H, br, 5-H and OH), 4.27—4.22 (1 H, m, 4′-H), 4.18 (1 H, dd, *J* 5.6 and 3.0 Hz, 3′-H), 3.48 (1 H, dd, *J* 9.0 and 5.6 Hz, 2′-H), 3.00—2.25 (6 H, m, 5′-H and CH_2CH_3), and 1.40—0.95 (6 H, m, CH_2CH_3).

The slower moving fraction was evaporated and the residue was recrystallised from ethanol to give compound (**2e**) (120 mg, 44%), m.p. 166—168 °C (Found: C, 48.9; H, 5.15; N, 10.35. $C_{11}H_{14}N_2O_4S$ requires C, 48.88; H, 5.22; N, 10.36%); $\lambda_{max.}$(EtOH) 225 (log ε 3.97) and 245 nm (3.88); *m/z* 270 (M^+); δ_H[$(CD_3)_2SO$] 7.93 (1 H, d, *J* 7.5 Hz, 6-H), 6.36 (1 H, d, *J* 5.3 Hz, 1′-H), 6.03 (1 H, d, *J* 4.8 Hz, OH), 5.91 (1 H, d, *J* 7.5 Hz, 5-H), 5.27 (1 H, dd, *J* 5.3 and 0.8 Hz, 2′-H), 4.50—4.05 (2 H, m, 3′- and 4′-H), 2.65—2.20 (4 H, m, 5′-H and CH_2CH_3), and 1.11 (3 H, t, *J* 6.8 Hz, CH_2CH_3).

1-(5-*Acetylthio*-5-*deoxy*-β-D-*arabinofuranosyl*)-2,2′-*anhydro*-5-*fluorouracil* (**2f**).—A solution of 2′,5′-dichloro-2′,5′-dideoxy-5-fluorouridine (**1b**) (300 mg, 1.0 mmol), thioacetic *S*-acid (76 mg, 1.0 mmol), and triethylamine (500 mg, 5.0 mmol) in DMF (30 ml) was heated at 100 °C for 4 h under an N_2 atmosphere. The mixture was evaporated under reduced pressure and the residue was chromatographed on a silica gel column eluting with chloroform–methanol (50:1). Recrystallisation of the product from ethanol gave compound (**2f**) (280 mg, 92%), m.p. 186—188 °C (Found: C, 43.9; H, 3.8; N, 9.3. $C_{11}H_{11}FN_2O_5S$ requires C, 43.71; H, 3.67; N, 9.27%); $\lambda_{max.}$(EtOH) 229 (log ε 4.01) and 245sh (3.99); *m/z* 302 (M^+); δ_H[$(CD_3)_2SO$] 8.32 (1 H, d, *J* 4.5 Hz, 6-H), 6.35 (1 H, d, *J* 5.7 Hz, 1′-H), 6.11 (1 H, br d, *J* 4.5 Hz, OH), 5.35 (1 H, br d, *J* 5.7 Hz, 2′-H), 4.50—4.00 (2 H, br, 3′- and 4′-H), 3.05—2.75 (2 H, m, 5′-H), and 2.32 (3 H, s, $COCH_3$).

Preparation of 1-(5-*Deoxy*-5-*phenylthio*-β-D-*arabinofuranosyl*)*uracil* (**3**) *by Reaction of* 1-(5-*Chloro*-5-*deoxy*-β-D-*arabinofuranosyl*)*uracil* (**7**) *with Thiophenol*.—A solution of 1-(5-chloro-5-deoxy-β-D-arabinofuranosyl)uracil (**7**)[8] (100 mg, 0.38 mmol), thiophenol (42 mg, 0.38 mmol), and triethylamine (200 mg, 2.0 mmol) in DMF (20 ml) was heated at 100 °C for 3.5 h under an N_2 atmosphere. The mixture was evaporated under reduced pressure and the residue was crystallised twice from water to give compound (**3**) (70 mg, 55%) which was identical with the product prepared above.

1-(2-O-*Acetyl*-3,5-*dideoxy*-3,5-*epithio*-β-D-*xylofuranosyl*)-*uracil* (**9a**).—A suspension of compound (**2b**) (150 mg, 0.53 mmol) in methanolic sodium methoxide [prepared from Na (120 mg, 5.2 mmol) in absolute methanol (30 ml)] was refluxed for 1 h. The solution was neutralised with Amberlite CG-50 (H^+) and the exchanger was washed with methanol. The mixture was evaporated under reduced pressure. Pyridine (3 ml) and acetic anhydride (3 ml) were added to the residue and the solution was stirred for 30 min at room temperature. The reaction mixture was poured into ice–water and the solution was extracted with chloroform. The chloroform layer was washed with saturated aqueous sodium hydrogen carbonate, saturated aqueous sodium hydrogen sulphate and water, evaporated under reduced pressure, and the residue crystallised twice from ethanol to give compound (**9a**) (100 mg, 67%), m.p. 192—193 °C (Found: C, 46.7; H, 4.35; N, 9.8. $C_{11}H_{12}N_2O_5S$ requires C, 46.47; H, 4.25; N, 9.85%); $\lambda_{max.}$(EtOH) 260 nm (log ε 4.00); *m/z* 284 (M^+); δ_H[270 Hz, $CDCl_3$] 8.34 (1 H, br s, HN^3), 8.15 (1 H, d, *J* 8.12 Hz, 6-H), 6.29 (1 H, d, *J* 3.42 Hz, 1′-H), 5.90

(1 H, dd, *J* 8.12 and 2.14 Hz, 5-H), 5.26—5.21 (2 H, m, 2'- and 4'-H), 4.03 (1 H, dd, *J* 5.56 Hz, 3'-H), 3.58 (1 H, dd, *J* 10.69 and 4.70 Hz, 5'-H), 2.90 (1 H, d, *J* 10.69 Hz, 5'-H), and 2.09 (3 H, s, $COCH_3$) [Decoupling the two-proton multiplet at 5.26—5.21 p.p.m. (2'-and 4'-H) causes the two doublets at 6.29 p.p.m. (1'-H) and 4.03 p.p.m. (3'-H) to collapse to two sharp singlets and the double doublet at 3.58 p.p.m. (5'-H) to collapse to a doublet. Decoupling the two doublets at 6.29 (1'-H) and 4.03 p.p.m. (3'-H) partially collapses the multiplet at 5.26—5.21 p.p.m. (2'- and 4'-H), respectively.] δ_C[25.00 MHz, $(CD_3)_2SO$] 169.78 (s), 163.28 (s), 150.41 (s), 140.27 (d), 102.44 (d), 91.03 (d), 83.02 (d), 82.55 (d), 45.05 (d), 29.60 (t), and 20.30 (q); $\nu_{max.}$(KBr) 1 745, 1 695, 1 235, and 1 060 cm^{-1}.

1-(3,5-*Dideoxy*-3,5-*epithio*-2-O-*methylsulphonyl*-β-D-*xylofuranosyl*)*uracil* (**9b**).—A suspension of compound (**2b**) (284 mg, 1.0 mmol) in methanolic sodium methoxide [prepared from Na (230 mg, 10 mmol) in absolute methanol (30 ml)] was refluxed for 1 h. The solution was neutralised with Amberlite CG-50 (H^+) and the exchanger was washed with methanol. The mixture was evaporated under reduced pressure and pyridine (2 ml) and methanesulphonyl chloride (1 ml) were added to the residue; the resulting solution was then stirred at room temperature for 1 h. After this it was poured into ice–water and the mixture extracted with chloroform. The chloroform layer was washed with saturated aqueous sodium hydrogen carbonate, saturated aqueous sodium hydrogen sulphate, and water, evaporated under reduced pressure, and the residue recrystallised from methanol to give compound (**9b**) (229 mg, 72%), m.p. 172 °C (Found: C, 37.3; H, 3.75; N, 8.6. $C_{10}H_{12}N_2O_6S_2$ requires C, 37.49; H, 3.78; N, 8.75%); $\lambda_{max.}$(EtOH) 260 nm (log ε 4.00); *m/z* 320 (M^+); δ_H[$(CD_3)_2SO$] 11.45 (1 H, br d, *J* 2.3 Hz, HN^3), 8.10 (1 H, d, *J* 8.3 Hz, 6-H), 6.14 (1 H, d, *J* 3.0 Hz, 1'-H), 5.79 (1 H, dd, *J* 8.3 and 2.3 Hz, 5-H), 5.48 (1 H, dd, *J* 3.0 and 1.5 Hz, 2'-H), 5.31 (1 H, dt, *J* 5.2 and 1.5 Hz, 4'-H), 4.29 (1 H, dd, *J* 5.7 and 1.5 Hz, 3'-H), 3.58 (1 H, dd, *J* 10.2 and 5.4 Hz, 5'-H), 3.28 (3 H, s, CH_3), and 3.04 (1 H, dd, *J* 10.2 and 1.0 Hz, 5'-H).

1-(2-O-*Acetyl*-3,5-*dideoxy*-3,5-*epithio*-β-D-*xylofuranosyl*)-5-*fluorouracil* (**9c**).—A suspension of compound (**2f**) (160 mg, 0.53 mmol) in methanolic sodium methoxide [prepared from Na (120 mg, 5.22 mmol) in absolute methanol (30 ml)] was refluxed for 1 h. The solution was neutralised with Amberlite CG-50 (H^+) and the exchanger was washed with methanol. The mixture was then evaporated under reduced pressure and pyridine (2 ml) and acetic anhydride (2 ml) were added to the residue; the solution was stirred for 24 h at room temperature. The reaction mixture was poured into ice–water and the solution was extracted with chloroform. The chloroform layer was washed with saturated aqueous sodium hydrogen carbonate, saturated aqueous sodium hydrogen sulphate and water, evaporated under reduced pressure, and the residue chromatographed on a silica gel column eluting with chloroform–methanol (50:1) to afford compound (**9c**) as a foam (128 mg, 80%), m.p. 67—72 °C (Found: C, 43.75; H, 3.9; N, 9.1. $C_{11}H_{11}FN_2O_5S$ requires C, 43.71; H, 3.67; N, 9.27%); $\lambda_{max.}$(EtOH) 266 nm (log ε 3.92); *m/z* 302 (M^+); δ_H[$CDCl_3$] 9.60—9.10 (1 H, br, HN^3), 8.39 (1 H, d, *J* 6.0 Hz, 6-H), 6.31 (1 H, dd, *J* 1.5 and 3.5 Hz, 1'-H), 5.40—5.13 (2 H, m, 2'- and 4'-H), 4.08 (1 H, dd, *J* 1.2 and 6.0 Hz, 3'-H), 3.62 (1 H, dd, *J* 11.3 and 6.3 Hz, 5'-H), 2.92 (1 H, dd, *J* 11.3 and 0.8 Hz, 5'-H), and 2.09 (3 H, s, $COCH_3$).

2,2'-*Anhydro*-1-(3,5-*dideoxy*-3,5-*epithio*-β-D-*lyxofuranosyl*)-*uracil* (**10**).—A suspension of compound (**9b**) (100 mg, 0.3 mmol) in methanolic sodium methoxide [prepared from Na (7 mg, 0.3 mmol) in absolute ethanol (10 ml)] was refluxed for 30 min. The solution was neutralised with Amberlite CG-50 (H^+) and the exchanger was washed with methanol. The mixture was then evaporated under reduced pressure and the residue recrystallised from water to give compound (**10**) (67 mg, 96%), m.p. 277—278 °C (Found: C, 47.8; H, 3.65; N, 12.2. $C_9H_8N_2O_3S$·0.1H_2O requires C, 47.82; H, 3.66; N, 12.39%); $\lambda_{max.}$(EtOH) 221 (log ε 3.97) and 251 nm (3.86); *m/z* 224 (M^+); δ_H[$(CD_3)_2SO$] 7.90 (1 H, d, *J* 7.6 Hz, 6-H), 6.40 (1 H, d, *J* 5.9 Hz, 1'-H), 5.92 (1 H, d, *J* 7.6 Hz, 5-H), 5.56 (1 H, dd, *J* 5.9 and 7.6 Hz, 2'-H), 5.24 (1 H, m, 4'-H), 4.46 (1 H, dd, *J* 7.6 and 6.6 Hz, 3'-H), 3.44 (1 H, dd, *J* 11.0 and 6.1 Hz, 5'-H), and 2.61 (1 H, dd, *J* 11.0 and 3.0 Hz, 5'-H).

1-(3,5-*Dideoxy*-3,5-*epithio*-β-D-*lyxofuranosyl*)*uracil* (**11**).—Compound (**10**) (50 mg, 0.22 mmol) was added to a solution of sodium hydroxide (10 mg, 0.25 mmol) in water (4 ml), and the suspension was stirred for 1.5 h. The solution was neutralised with Amberlite CG-50 (H^+) and the exchanger was washed with water. The mixture was evaporated under reduced pressure and the residue recrystallised from ethanol to give compound (**11**) (35 mg, 65%), m.p. 243 °C (Found: C, 44.5; H, 4.15; N, 11.5. $C_9H_{10}N_2O_4S$ requires C, 44.62; H, 4.16; N, 11.56%); $\lambda_{max.}$(EtOH) 261 nm (log ε 4.02); *m/z* 242 (M^+); δ_H[$(CD_3)_2SO$] 11.60—10.09 (1 H, br, HN^3), 8.22 (1 H, d, *J* 8.3 Hz, 6-H), 6.14 (1 H, d, *J* 5.1 Hz, 1'-H), 6.00—5.55 (2 H, br, 5-H and OH), 4.88 (1 H, dt, *J* 5.9 and 1.7 Hz, 4'-H), 4.70—4.10 (2 H, br, 2'- and 3'-H), 3.50 (1 H, dd, *J* 10.4 and 5.3 Hz, 5'-H), and 2.83 (1 H, dd, *J* 10.4 and 2.3 Hz, 5'-H).

1-(2-O-*Acetyl*-3,5-*dideoxy*-3,5-*epithio*-β-D-*xylofuranosyl*)-*uracil S-Oxide* (**12**).—A suspension of compound (**9a**) (284 mg, 1.0 mmol) and *m*-chloroperbenzoic acid (175 mg, 1.0 mmol) in chloroform (30 ml) was stirred for 30 min at room temperature. An appropriate amount of Pd–C was added to the solution, and the excess of *m*-chloroperbenzoic acid was deactivated with stirring for 10 min. The mixture was filtered, the filtrate evaporated under reduced pressure, and the residue recrystallised from ethanol to give compound (**12**) (240 mg, 80%), m.p. 159—160 °C (Found: C, 44.5; H, 4.15; N, 11.5. $C_{11}H_{12}N_2O_6S$ requires C, 44.62; H, 4.16; N, 11.56%); $\lambda_{max.}$(EtOH) 257 nm (log ε 4.02); *m/z* 300 (M^+); δ_H[$(CD_3)_2SO$] 11.42 (1 H, br, HN^3), 7.90 (0.7 H, d, *J* 8.3 Hz, 6-H), 7.65 (0.3 H, d, *J* 8.3 Hz, 6-H), 6.21 (1 H, d, *J* 6.2 Hz, 1'-H), 6.00—5.00 (3 H, m, 5-, 2'-, and 4'-H), 4.50—3.60 (2 H, m, 3'- and 5'-H), 2.95 (1 H, br, 5'-H), and 2.06 (3 H, s, $COCH_3$).

1-(2-O-*Acetyl*-3,5-*dideoxy*-3,5-*epithio*-β-D-*xylofuranosyl*)-*uracil* S-*Dioxide* (**13**).—A suspension of compound (**12**) (100 mg, 0.33 mmol) and *m*-chloroperbenzoic acid (60 mg, 0.34 mmol) in chloroform (10 ml) was stirred for 4 h at room temperature. The resulting precipitate was filtered off and recrystallised from methanol to give compound (**13**) (95 mg, 90%), m.p. 283 °C (Found: C, 41.9; H, 3.75; N, 9.05. $C_{11}H_{12}N_2O_7S$ requires C, 41.77; H, 3.82; N, 8.86%); $\lambda_{max.}$(EtOH) 257 nm (log ε 3.99); *m/z* 317 ($M^+ + 1$); δ_H[$(CD_3)_2SO$] 11.49 (1 H, br, HN^3), 7.58 (1 H, d, *J* 8.1 Hz, 6-H), 6.25 (1 H, d, *J* 6.4 Hz, 1'-H), 5.87 (1 H, d, *J* 8.1 Hz, 5-H), 5.46 (1 H, dd, *J* 6.1 and 2.4 Hz, 2'-H), 5.32—5.23 (1 H, m, 4'-H), 5.03 (1 H, t, *J* 5.4 Hz, 3'-H), 4.60 (1 H, dd, *J* 14.7 and 1.5 Hz, 5'-H), 4.25 (1 H, d, *J* 14.7 Hz, 5'-H), and 2.05 (3 H, s, $COCH_3$).

Preparation of Compound (**13**) *by Oxidation of Compound* (**9a**).—A suspension of compound (**9a**) (100 mg, 0.35 mmol) and *m*-chloroperbenzoic acid (182 mg, 1.05 mmol) in chloroform (10 ml) was stirred for 2.5 h at room temperature. The resulting precipitate was filtered off and recrystallised from methanol to give compound (**13**) (72 mg, 65%), which was identical with the product prepared above.

2,2′-*Anhydro*-1-(5-*deoxy*-5-*mercapto*-β-D-*arabinofuranosyl*)-*uracil* (**14**).—A suspension of compound (**2b**) (284 mg, 1.0 mmol) and triethylamine (300 mg, 3.0 mmol) in methanol (30 ml) was refluxed for 30 min. The mixture was then evaporated under reduced pressure and the residue was twice crystallised from methanol to give compound (**14**) (150 mg, 62%), m.p. 179 °C (Found: C, 44.3; H, 4.5; N, 11.2. $C_9H_{10}N_2O_4S\cdot 0.3CH_3OH$ requires C, 44.32; H, 4.52; N, 11.08%); $\lambda_{max.}$(EtOH) 225 (log ε 4.00) and 246 nm (3.90); *m/z* 242 (M^+); δ_H[$(CD_3)_2SO$], 7.95 (1 H, d, *J* 7.5 Hz, 6-H), 6.38 (1 H, d, *J* 5.4 Hz, 1′-H), 6.04 (1 H, d, *J* 7.5 Hz, 5-H), 5.95 (1 H, d, *J* 7.5 Hz, OH), 5.31 (1 H, d, *J* 5.4 Hz, 2′-H), 4.48 (1 H, br, 3′-H), 4.38—3.95 (1 H, br, 4′-H), and 2.65—2.30 (3 H, m, 5′-H and SH).

1-(3-O-*Acetyl*-5-*acetylthio*-5-*deoxy*-β-D-*arabinofuranosyl*)-2,2′-*anhydrouracil* (**15**).—A solution of compound (**14**) (100 mg, 0.41 mmol) in pyridine (1 ml) and acetic anhydride (1 ml) was stirred for 1 h at room temperature. The mixture was then evaporated under reduced pressure and the residue chromatographed on a silica gel column eluting with chloroform–methanol (30:1) to afford compound (**15**) after recrystallisation from ethanol (91 mg, 68%), m.p. 160 °C (Found: C, 47.65; H, 4.4; N, 8.55. $C_{13}H_{14}N_2O_6S$ requires C, 47.85; H, 4.32; N, 8.58%); $\lambda_{max.}$(EtOH) 226 (log ε 4.11) and 248 nm (3.92); *m/z* 326 (M^+); δ_H[$CDCl_3$] 7.50 (1 H, d, *J* 7.8 Hz, 6-H), 6.45 (1 H, d, *J* 5.7 Hz, 1′-H), 6.04 (1 H, d, *J* 7.8 Hz, 5-H), 5.50 (1 H, d, *J* 5.7 Hz, 2′-H), 5.37 (1 H, d, *J* 1.5 Hz, 3′-H), 4.43 (1 H, dt, *J* 6.8 and 1.5 Hz, 4′-H), 2.98 (2 H, d, *J* 6.8 Hz, 5′-H), 2.33 (3 H, s, S-$COCH_3$), and 2.16 (3 H, s, $OCOCH_3$).

Preparation of Compound (**15**) *by Acetylation of Compound* (**2b**).—A solution of compound (**2b**) (100 mg, 0.35 mmol) in pyridine (1 ml) and acetic anhydride (1 ml) was stirred for 1 h at room temperature. The mixture was evaporated under reduced pressure and the residue was twice recrystallised from ethanol to give compound (**15**) (60 mg, 52%), which was identical with the product prepared above.

1-(3,5-*Dideoxy*-3,5-*epidithio*-β-D-*xylofuranosyl*)*uracil* (**16a**).—A suspension of compound (**9a**) (100 mg, 0.35 mmol) and sodium disulphide (70%; 45 mg, 0.56 mmol) in ethanol was refluxed for 24 h under an N_2 atmosphere. The mixture was evaporated under reduced pressure and the residue was chromatographed on a silica gel column eluting with chloroform–methanol (5:1). The appropriate fractions were collected and evaporated under reduced pressure. The residue was dissolved in 0.1M aqueous sodium hydroxide and the solution was filtered. The filtrate was neutralised with acetic acid and the resulting precipitate was filtered off to afford compound (**16a**) (16 mg, 17%), m.p. 257—258 °C (Found: C, 39.2; H, 3.65; N, 9.8. $C_9H_{10}N_2O_4S_2\cdot 0.2H_2O$ requires C, 38.89; H, 3.82; N, 10.08%); $\lambda_{max.}$(EtOH) 260 nm (log ε 3.98); *m/z* 274 (M^+); δ_H[$(CD_3)_2SO$] 11.44 (1 H, br s, HN^3), 7.44 (1 H, d, *J* 8.0 Hz, 6-H), 6.07 (1 H, d, *J* 5.4 Hz, OH), 5.80—5.60 (2 H, br, 1′- and 5-H), 5.14 (1 H, m, 4′-H), 4.17—3.84 (2 H, m, 3′- and 2′-H), 3.43 (1 H, d, *J* 13.2 Hz, 5′-H), and 2.91 (1 H, dd, *J* 13.2 and 4.3 Hz, 5′-H).

Preparation of Compound (**16a**) *by Reaction of Compound* (**2b**) *with Sodium Disulphide*.—A suspension of compound (**2b**) (100 mg, 0.35 mmol) and sodium disulphide (70%) (60 mg, 0.75 mmol) in ethanol (20 ml) was refluxed for 24 h under an N_2 atmosphere. The mixture was evaporated under reduced pressure and the residue was chromatographed on a silica gel column eluting with chloroform–methanol (5:1). The appropriate fractions were collected and evaporated under reduced pressure and the residue was dissolved in 0.1M aqueous sodium hydroxide. The solution was neutralised with acetic acid and the resulting precipitate was filtered off to afford compound (**16a**) (38 mg, 39%), which was identical with the product prepared above.

Preparation of Compound (**16a**) *by Reaction of* 2′,5′-*Dichlorouridine* (**1a**) *with Sodium Disulphide*.—A suspension of compound (**1a**) (281 mg, 1.0 mmol) and sodium disulphide (70%; 240 mg, 3.0 mmol) in ethanol (30 ml) was refluxed for 24 h under an N_2 atmosphere. The mixture was evaporated under reduced pressure and the residue was chromatographed on a silica gel column eluting with chloroform–methanol (5:1). The appropriate fractions were collected and evaporated under reduced pressure and the residue was dissolved in 0.1M aqueous sodium hydroxide. The solution was neutralised with acetic acid and the resulting precipitate was filtered off to afford compound (**16a**) (53 mg, 19%), which was identical with the product prepared above.

Acetylation of Compound (**16a**).—A solution of compound (**16a**) (55 mg, 0.2 mmol) in pyridine (1 ml) and acetic anhydride (1 ml) was stirred for 1 h at room temperature. The reaction mixture was poured into ice–water and the resulting precipitate was filtered off and recrystallised from ethanol–acetone to give compound (**16b**) (57 mg, 90%), m.p. 280 °C (decomp.) (Found: C, 41.6; H, 3.75; N, 8.85. $C_{11}H_{12}N_2O_5S_2$ requires C, 41.76; H, 3.82; N, 8.86%); $\lambda_{max.}$(EtOH) 260 nm (log ε 3.95); *m/z* 316 (M^+); δ_H[$(CD_3)_2SO$] 11.47 (1 H, br, HN^3), 7.56 (1 H, d, *J* 8.3 Hz, 6-H), 5.97 (1 H, d, *J* 6.6 Hz, 1′-H), 5.76 (1 H, d, *J* 8.3 Hz, 5-H), 5.27 (1 H, dd, *J* 6.6 and 3.7 Hz, 4′-H), 5.06 (1 H, t, *J* 6.1 Hz, 2′-H), 4.42 (1 H, t, *J* 6.1 Hz, 3′-H), 3.56 (1 H, d, *J* 13.2 Hz, 5′-H), 2.99 (1 H, dd, *J* 13.2 and 3.9 Hz, 5′-H), and 2.06 (3 H, s, $COCH_3$).

5,6-*Dihydro*-1-(3,5-*dideoxy*-5-*phenylthio*-6,3′-*epithio*-β-D-*xylofuranosyl*)*uracil* (**17**).—A suspension of compound (**9a**) (284 mg, 1.0 mmol) and thiophenol (300 mg, 2.7 mmol) in ethanolic sodium ethoxide [prepared from Na (50 mg, 2.2 mmol) in absolute ethanol (30 ml)] was refluxed for 22 h under an N_2 atmosphere. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column eluting with chloroform–methanol (10:1). The appropriate fractions were collected and evaporated under reduced pressure to afford compound (**17**) after recrystallisation from methanol (102 mg, 29%), m.p. 233—234 °C (Found: C, 50.9; H, 4.55; N, 7.75. $C_{15}H_{16}N_2O_4S_2$ requires C, 51.12; H, 4.58; N, 7.95%); $\lambda_{max.}$(EtOH) 252 nm (log ε 3.90); $\lambda_{max.}$(pH > 12) 256 (log ε 4.24); *m/z* 352 (M^+); δ_H[$(CD_3)_2SO$] 10.67 (1 H, br, HN^3), 7.51—7.06 (5 H, m, S-Ph), 6.00 (1 H, d, *J* 3.0 Hz, OH), 5.87 (1 H, s, 1′-H), 5.06 (1 H, dd, *J* 10.0 and 6.0 Hz, 6-H), 4.51 (1 H, m, 4′-H), 4.17 (1 H, d, *J* 3.0 Hz, 2′-H), 3.47 (3 H, br, 3′- and 5′-H), 2.81 (1 H, dd, *J* 6.0 and 16.0 Hz, 5-H), and 2.61 (1 H, dd, *J* 10.0 and 16.0 Hz, 5-H).

References

1 Part 5, K. Hirota, T. Tomishi, and Y. Maki, *J. Chem. Soc., Perkin Trans. 1*, 1988, preceding paper. This paper is also considered as Part 60 of a series entitled Pyrimidines.

2 A part of this work was reported preliminarily: K. Hirota, Y. Kitade, T. Tomishi, and Y. Maki, *J. Chem. Soc., Chem. Commun.*, 1987, 1801.

3 K. Hirota, Y. Kitade, F. Iwami, S. Senda, and Y. Maki, *Synthesis*, 1983, 121; K. Hirota, Y. Kitade, F. Iwami, and S. Senda, *Chem. Pharm. Bull.*, 1984, **32**, 2591.

4 K. Hirota, Y. Kitade, T. Tomishi, and Y. Maki, *J. Chem. Soc., Chem. Commun.*, 1984, 108; K. Hirota, Y. Kitade, T. Tomishi, and Y. Maki, *Chem. Pharm. Bull.*, 1985, **33**, 4212.

5 K. Hirota, Y. Kitade, T. Tomishi, and Y. Maki, *Nucleosides, Nucleotides*, 1985, **4**, 681.

6 E. Block in 'Comprehensive Heterocyclic Chemistry,' eds. A. Katritzky and C. W. Rees, Pergamon Press, Oxford, vol. 7, p. 403.

7 I. Wempen and J. J. Fox, *J. Org. Chem.*, 1969, **34**, 1020.
8 H. Hřebabecký and J. Beránek, *Collect. Czech. Chem. Commun.*, 1978, **43**, 3268.
9 K. J. Divakar and C. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1625; A. Matsuda and T. Miyasaka, *Heterocycles*, 1983, **20**, 55.
10 T. Ho, 'Hard and Soft Acids and Bases Principle in Organic Chemistry,' Academic Press, New York, 1977.
11 D. M. Brown, C. B. Parihar, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 1958, 3028.
12 B. Bannister and F. Kagan, *J. Am. Chem. Soc.*, 1960, **85**, 3363; R. W. Chambers and V. Kurkov, *ibid.*, 1963, **85**, 2160.
13 M. Imazawa, T. Ueda, and T. Ukita, *Chem. Pharm. Bull.*, 1975, **23**, 604.
14 E. De Clercq, J. Descamps, P. Somer, and A. Holý, *Science*, 1978, **200**, 563; E. De Clercq and A. Holý, *J. Med. Chem.*, 1979, **22**, 510; R. A. Smith, V. Knight, and J. A. D. Smith, eds. 'Clinical Applications of Ribavirin,' Academic Press, New York, 1984; D. E. Bergstrom, A. J. Brattesani, M. K. Ogawa, P. A. Reddy, M. J. Schweickert, J. Bal, and E. De Clercq, *J. Med. Chem.*, 1984, **27**, 285; E. De Clercq and J. A. Montgomery, *Antiviral Res.*, 1983, **3**, 17.

Received 28*th October* 1987; *Paper* 7/1918