Synthesis of Some 5-Halogenovinyl Derivatives of Uracil and their Conversion into 2'-Deoxyribonucleosides

By **Philip J. Barr, A. Stanley Jones,*** **Gabriel Verhelst,** and **Richard T. Walker,** Chemistry Department, University of Birmingham, Birmingham B15 2TT

Treatment of 5-formyluracil with malonic acid in the presence of piperidine gave (E)-5-(2-carboxyvinyl)uracil which, upon reaction with the appropriate N-halogenosuccinimide, gave (E)-5-(2-bromovinyl)uracil, (E)-5-(2-chlorovinyl)uracil, and (E)-5-(2-iodovinyl)uracil. The last mentioned compound was also obtained by the action of iodine chloride on 5-vinyluracil. 5-(1-Chlorovinyl)uracil upon treatment with bromine gave 5(2-bromo-1-chlorovinyl)uracil which reacted with sodium methoxide to give 5-bromoethynyluracil. (E)-5-(2-Bromovinyl)-uracil was converted into its trimethylsilyl derivative which was condensed with 2-deoxy-3,5-di-O-(p-toluoyl)-α-D-$erythro$-pentofuranosyl chloride to give the α- and β-anomers of the blocked deoxyribonucleoside. Removal of the p-toluoyl blocking groups with sodium methoxide afforded (E)-5-(2-bromovinyl)-1-(2-deoxy-α-D-$erythro$-pentofuranosyl)uracil and (E)-5-(2-bromovinyl)-2'-deoxyuridine. A similar series of reactions gave (E)-5-(2-iodovinyl)-2'-deoxyuridine and 5-(2-bromo-1-chlorovinyl)-2'-deoxyuridine. 5-(1-Chlorovinyl)uracil could be condensed similarly with the blocked sugar derivative to give the α- and β-anomers of the blocked deoxyribonucleoside. Attempted removal of the groups with sodium methoxide gave 2'-deoxy-5-ethynyluridine and mild treatment with methanolic ammonia gave the same product and some 2'-deoxy-5-ethynyl-5'-O-(p-toluoyl)-uridine. 5-(1-Chlorovinyl)-2'-deoxyuridine was obtained by the addition of HCl to 2'-deoxy-5-ethynyluridine. Aspects of the elimination reactions of 5-(halogenovinyl)uracil derivatives are discussed.

(E)-2'-DEOXY-5-(2-HALOGENOVINYL)URIDINES are potent inhibitors of herpes-simplex viruses, the bromo-derivative being the most active compound against the herpes-simplex virus-type 1 yet discovered.[1] This compound shows extremely low toxicity, is effective in the treatment of herpes-simplex infections in animals,[2] and is showing promise in preliminary clinical trials.[3] So far, chemical syntheses of this and related compounds have been mentioned only briefly.[1,4] Herein we report details of their syntheses and of the 5-(halogenovinyl)-uracils from which they are made.

(E)-5-(2-Halogenovinyl)uracils were obtained from 5-vinyluracil (1); the procedure for obtaining the bromo-compound (2) by treatment of the uracil (1) with bromine in dimethylformamide (DMF) has already been described.[5] The corresponding iodo-compound (3) was obtained in a similar manner by the use of iodine chloride. An alternative route to these compounds was *via* 5-formyluracil (6) which, upon treatment with malonic acid in the presence of piperidine, gave (E)-5-(2-carboxy-vinyl)uracil (4). Treatment of the latter with N-bromosuccinimide and with N-chlorosuccinimide in aqueous solution gave the (E)-5-(2-halogenovinyl)-uracils (2) and (5), respectively. The corresponding iodo-compound (3) was obtained by treatment of compound (4) with N-iodosuccinimide in DMF. The assignment of the E-configuration to the compounds (2), (4), and (5) is based upon the coupling constants of the vinylic protons which are 13, 15, and 15 Hz, respectively. The chemical shifts of the vinylic protons of the iodo-compound (3) are the same, so no coupling is apparent. Since, however, the trimethylsilyl derivative and the 2'-deoxyribonucleoside obtained from (3) show coupling constants of 15 Hz for the vinylic protons, it can be concluded that this too has an E-configuration.

In the reactions which form the halogen-containing derivatives, (2), (3), and (5), from the carboxylic acid

(4), only traces of the corresponding Z-isomers were formed. This is somewhat surprising, since halogenation of analogous E-carboxyvinyl compounds gives, in relatively non-polar solvents such as acetone, the Z-halogenovinyl derivative and in polar solvents a mixture of the Z- and E-isomers.[6-10]

5-(1-Chlorovinyl)uracil (7) was obtained from 5-acetyluracil by the procedure previously described.[11] The product was identical with a sample previously obtained, but the u.v. spectra were not as recorded.

(1) X = H
(2) X = Br
(3) X = I
(4) X = CO$_2$H
(5) X = Cl

(6) R = CHO
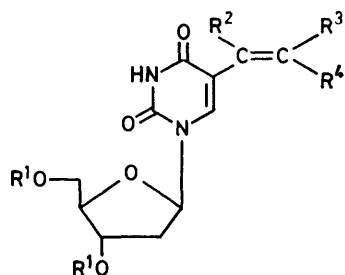(7) R = CCl=CH$_2$
(8) R = CCl=CHBr
(9) R = C≡CBr
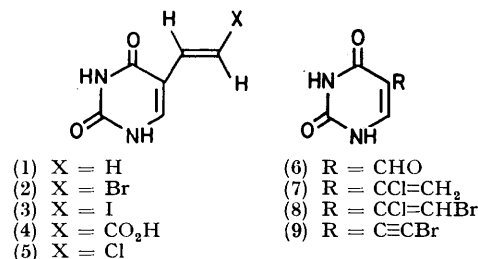
Corrected values are now given (see Experimental section). Treatment of compound (7) with bromine gave 5-(2-bromo-1-chlorovinyl)uracil (8) presumably by the addition of bromine and subsequent elimination of hydrogen bromide. The structure assigned to this compound is based upon its elemental analysis and mass and ^{1}H n.m.r. spectra, but the stereochemistry around the ethylenic double bond was not determined.

Compound (8), upon treatment with sodium methoxide in methanol, gave 5-bromoethynyluracil (9), the structure of which was derived from its elemental analysis, its ^{1}H n.m.r. spectrum, which shows the presence of only one proton (H-6) in addition to the NH protons, and its ^{13}C n.m.r. spectrum, which shows the presence of six types of carbon atom, the chemical shifts of which are as follows (those of 5-ethynyluracil in parentheses): C-2, 150.5 (150.6); C-4, 162.9 (170.0); C-5, 96.7 (96.4);

C-6, 147.0 (146.6); C≡, 73.0 (83.3); and ≡CBr, 54.0 (≡CH, 76.6). These assignments are based upon the values given for the carbon atoms of 5-substituted uracils by Tarpley and Goldstein [12] and, for the ethynyl carbon atoms, with those given for hex-1-yne and 1-bromohex-1-yne by Traficante and Maciel.[13] The mass spectrum of (9) is also consistent with the assigned structure.

To obtain the 2′-deoxyribonucleosides from the 5-(halogenovinyl)uracils, the latter were converted into their trimethylsilyl derivatives which were then condensed with 2-deoxy-3,5-di-O-(p-toluoyl)-α-D-erythro-pentofuranosyl chloride to give, in each case, a mixture of the α- and β-anomers of the blocked 2′-deoxyribonucleosides, the structures of which were established by ^{1}H n.m.r. spectroscopy. The condensation of the trimethylsilyl derivative of (E)-5-(2-bromovinyl)uracil was carried out in 1,2-dichloroethane with no added catalyst. An 88% yield of blocked 2′-deoxyribonucleosides was obtained and the ratio of β- to α-anomer was 1 : 1.3. Separation of the mixture by column chromatography gave pure samples of the anomers [(10) and (18) respec-
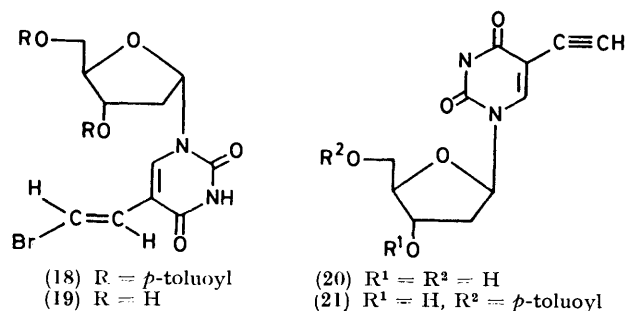

(18) R = p-toluoyl
(19) R = H

(20) R¹ = R² = H
(21) R¹ = H, R² = p-toluoyl

tively]. Removal of the p-toluoyl blocking groups with sodium methoxide gave (E)-5-(2-bromovinyl)-2′-deoxyuridine (11) and (E)-5-(2-bromovinyl)-1-(2-deoxy-α-D-erythro-pentofuranosyl)uracil (19), respectively. A similar series of reactions was carried out with (E)-5-(2-iodovinyl)uracil to give, finally, 2′-deoxy-(E)-5-(2-indovinyl)uridine (12). The overall yield was low, however, and the α-anomer was not isolated. The condensation of the trimethylsilyl derivative of 5-(2-bromo-1-chlorovinyl)uracil was carried out in the presence of mercury(II) bromide as catalyst. The required blocked 2′-deoxyribonucleoside (15) was obtained in 34% yield by fractional crystallisation of the mixture of anomers. The α-anomer was not characterised completely. Removal of the p-toluoyl blocking groups from (13) in the usual manner gave 5-(2-bromo-1-chlorovinyl)-2′-deoxyuridine (14) in 78% yield.

The condensation of the trimethylsilyl derivative of 5-(1-chlorovinyl)uracil gave, as in the previous cases, a mixture of the α- and β-anomers of the deoxyribonucleoside from which the β-anomer (15) was obtained by

(10) R¹ = p-toluoyl, R² = R⁴ = H, R³ = Br
(11) R¹ = R² = R⁴ = H, R³ = Br
(12) R¹ = R² = R⁴ = H, R³ = I
(13) R¹ = p-toluoyl, R² = Cl, R³,R⁴ = H, Br
(14) R¹ = H, R² = Cl, R³,R⁴ = H, Br
(15) R¹ = p-toluoyl, R² = Cl, R³ = R⁴ = H
(16) R¹ = R³ = R⁴ = H, R² = Cl
(17) R¹ = R³ = R⁴ = H, R² = COMe

column chromatography. However, attempts to remove the p-toluoyl groups with sodium methoxide gave 2′-deoxy-5-ethynyluridine (20). Methanolic ammonia was used in an attempt to avoid this elimination reaction, but this gave a 51% yield of (20) and a 13% yield of a

product, the n.m.r. spectrum and elemental analysis of which show it to be 2′-deoxy-5-ethynyl-5′-O-(p-toluoyl)-uridine (21). The assignment of the p-toluoyl group to the 5′-O-position is based upon the fact that the n.m.r. signal for the 5′-protons (δ 4.44) is similar to that for 2′-deoxy-5-ethynyl-3′,5′-di-O-(p-toluoyl)uridine (δ 4.58) and different from that for 2′-deoxy-5-ethynyluridine (δ 3.69). Formation of the 5′-O-acylated nucleoside upon partial deacylation of a protected nucleoside has been encountered previously in the case of 5-acetyl-uridine derivatives.[14] 5-(1-Chlorovinyl)-2′-deoxyuridine (16) was obtained in 65% yield, however, by the action of hydrochloric acid on 2′-deoxy-5-ethynyluridine (20). Some 5-acetyl-2′-deoxyuridine (17) was also produced in this reaction. It has already been shown [15] that (17) is produced in good yield by the action of dilute sulphuric acid on (20).

In order to synthesise 5-bromoethynyl-2′-deoxyuridine an unsuccessful attempt was made to obtain the trimethylsilyl derivative of 5-bromoethynyluracil. The conditions used led to extensive decomposition, however. In view of the ready elimination of hydrogen chloride from 5-(2-bromo-1-chlorovinyl)uracil (8) to give 5-bromoethynyluracil (9) by the action of sodium methoxide, attempts were made to effect a similar elimination from 5-(2-bromo-1-chlorovinyl)-2′-deoxyuridine (14) or its p-toluoyl derivative (13). The halogenovinyl side-chain was remarkably resistant to sodium methoxide in methanol at room temperature, and when more drastic conditions were used, unidentified products were obtained.

The elimination reactions of 5-(halogenovinyl)uracils and their 2′-deoxyribonucleosides are worthy of mention. The elimination of hydrogen chloride from 5-(1-chloro-vinyl)-2′-deoxyuridine (16) to give 2′-deoxy-5-ethynyl-uridine (20) proceeds much more readily than does the formation of a simple alkyne. This can be rationalised by invoking the participation of the substituted pyrimidine ring as in Scheme 1.

However, elimination of hydrogen chloride from 5-(2-bromo-1-chlorovinyl)-2′-deoxyuridine (14) is not so easy. It has been shown recently (King, Verhelst, and

De Clercq; unpublished results) that (14) has the Z-configuration (22), so the reason for the non-participation of the pyrimidine ring in this case is not clear.
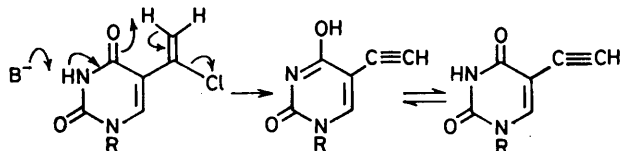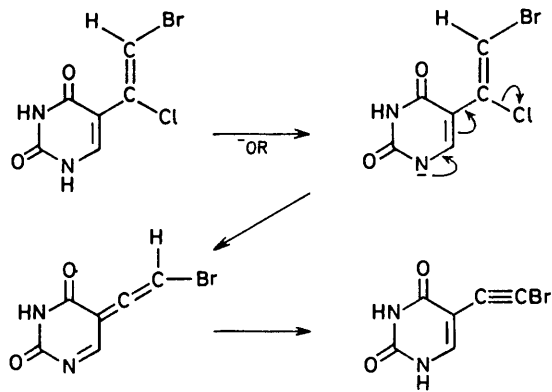

SCHEME 1

The products of the reaction of sodium alkoxides with (14) were not identified, but their n.m.r. spectra showed the presence of alkoxy-groups. This suggests that substitution rather than elimination had taken place. Why
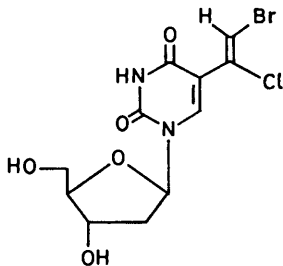
this should be so when 5-(2-bromo-1-chlorovinyl)uracil (8) gives 5-bromoethynyluracil (9) can be rationalised by suggesting that in the latter case the pyrimidine ring is involved to give an intermediate allene as in Scheme 2.

SCHEME 2

Participation of the pyrimidine ring in this manner is not possible with the nucleoside (14), but we can offer no logical explanation why the pyrimidine ring cannot participate in the same way as has been postulated above in the case of the elimination of hydrogen chloride from 5-(1-chlorovinyl)-2'-deoxyuridine (20).

EXPERIMENTAL

N.m.r. spectra were recorded at 100 MHz in $(CD_3)_2SO$ unless otherwise stated. T.l.c. was carried out on silica gel (MN Kieselgel G/UV_{254}; Machery, Nagel and Co., W. Germany) and column chromatography on Kieselgel 60 (70—120 mesh ASTM, type 7734; E. Merck A.G., W. Germany).

(E)-5-(2-*Carboxyvinyl*)*uracil* (4).—5-Formyluracil (6) [16] (3.65 g) was suspended in dry pyridine (10 ml) and malonic acid (2.35 g) and piperidine (0.5 ml) was then added. The mixture was heated on a steam-bath until the evolution of CO_2 ceased (2 h). The pyridine was removed by evaporation under reduced pressure and the residue dissolved in $2M$ NaOH (200 ml). The solution was filtered and the filtrate acidified to pH 4 with $1M$ HCl and cooled to 4 °C. The resulting crystalline solid was filtered off to give (E)-5-(2-*carboxyvinyl*)*uracil* (4) (3.3 g, 78%) (Found: C, 44.4; H, 3.3; N, 15.1. $C_7H_6N_2O_4 \cdot 0.25H_2O$ requires C, 44.8; H, 3.49; N, 14.9%); $\lambda_{max.}$ 299 (ε 20 260) and 268 nm (16 320); $\lambda_{min.}$ 278 nm (ε 15 770) in acidic ethanol; $\lambda_{max.}$ 300 (ε 17 080) and 264 nm (13 290); $\lambda_{min.}$ 274 nm (ε 12 340) in ethanol; $\lambda_{max.}$ 326 (ε 20 810) and 278 nm (15 410); $\lambda_{min.}$ 295 nm (ε 12 130) in alkaline ethanol; δ 3.50 (1 H, br s, $-CO_2H$), 6.75 (1 H, d, J 15 Hz, vinylic H), 7.31 (1 H, d, J 15 Hz, vinylic H), 7.97 (1 H, s, 6-H), and 11.3 (2 H, br s, NH).

(E)-5-(2-*Iodovinyl*)*uracil* (3).—(a) To a solution of 5-vinyluracil [17] (1.1 g) in dry DMF (40 ml) there was added a solution of iodine monochloride (1.28 g) in dry DMF (20 ml). The solution was kept at ca. 20 °C for 30 min and then at 100 °C for 30 min. It was then evaporated to dryness and the oily residue treated with water to give a solid. This was filtered off and dried to give (E)-5-(2-*iodovinyl*)*uracil* (3) (1.6 g, 76%) (Found: C, 27.2; H, 1.9; N, 10.7. C_6H_5-IN_2O_2 requires C, 27.3; H, 1.9; N, 10.6%); $\lambda_{max.}$ 294 (ε 9 900) and 250 nm (15 200); $\lambda_{min.}$ 278 nm (ε 9 250) at pH 1; $\lambda_{max.}$ 310 (ε 12 200) and 262 nm (15 850); $\lambda_{min.}$ 290 nm (ε 10 050) at pH 13; δ 7.18 (2 H, s, vinylic H), 7.68 (1 H, s, 6-H), and 11.1 (2 H, br s, NH).

(b) (E)-5-(2-Carboxyvinyl)uracil (364 mg) was dissolved in dry DMF (20 ml) and potassium acetate (200 mg), and N-iodosuccinimide (450 mg) was then added. The mixture was stirred at room temperature for 1 h and the solvent removed under reduced pressure and water (20 ml) was added to the residue. The resulting solid was filtered off and crystallised from water–methanol to give (E)-5-(2-iodovinyl)uracil (320 mg, 62%) which was identical with the product obtained by method (a).

(E)-5-(2-*Chlorovinyl*)*uracil* (5).—E-5-(2-Carboxyvinyl)-uracil (364 mg) was dissolved in water (15 ml) containing potassium acetate (200 mg), by heating. The solution was brought to ca. 90 °C and N-chlorosuccinimide (267 mg) was added in small portions. After the addition the mixture was stirred while cooling to room temperature and then cooled further to 4 °C. The solid which separated was filtered off and dried to give (E)-5-(2-*chlorovinyl*)*uracil* (5) (245 mg, 72%) (Found: C, 41.8; H, 2.8; N, 16.2. C_6H_5-ClN_2O_2 requires C, 41.8; H, 2.92; N, 16.2%); $\lambda_{max.}$ 291 (ε 9 610) and 248 nm (14 720); $\lambda_{min.}$ 268 nm (ε 5 880) in ethanol; δ 6.56 (1 H, d, J 13 Hz, vinylic H), 7.14 (1 H, d, J 13 Hz, vinylic H), 7.60 (1 H, d, 6-H), and 11.2 (2 H, br s, NH).

(E)-5-(2-*Bromovinyl*)*uracil* (2).—(E)-5-(2-Carboxyvinyl)-uracil was treated as described above, but N-bromosuccinimide was used. (E)-5-(2-Bromovinyl)uracil, identical with the compound previously prepared,[5] was obtained in 81% yield.

5-(1-*Chlorovinyl*)*uracil* (7).—This compound was obtained from 5-acetyluracil by the three-stage procedure described before.[11] The product has identical chromatographic properties and n.m.r. spectrum to those previously reported for this compound, but the u.v. spectra are different. The u.v. spectra of the original sample were redetermined and

found to be different from those reported. The modified values are $\lambda_{max.}$ 242 (ε 8 760) and 282 nm (7 720); $\lambda_{min.}$ 260 nm (ε 5 180) at pH 1; $\lambda_{max.}$ 242 (ε 8 220), and 282 nm (7 690); $\lambda_{min.}$ 260 nm (ε 4 710) at pH 6; $\lambda_{max.}$ 244 (ε 7 080) and 304 nm (6 370); $\lambda_{min.}$ 268 nm (ε 2 390) at pH 11.

5-(2-Bromo-1-chlorovinyl)uracil (8).—A solution of bromine (678 mg) in dry DMF (5 ml) was added to a solution of 5-(1-chlorovinyl)uracil (730 mg) in dry DMF (15 ml). The mixture was stirred at room temperature for 2 d and then heated on a steam-bath for 5 h. After being cooled to room temperature, the solution was poured into water (50 ml) and the resulting precipitate was filtered off to give 5-(2-*bromo*-1-*chlorovinyl*)*uracil* (8) (0.83 g) (yield 83%; a further 0.05 g being obtained upon concentration of the filtrate), m.p. >300 °C (Found: C, 28.5; H, 1.5; N, 11.3. $C_6H_4BrClN_2O_2$ requires C, 28.6; H, 1.60; N, 11.1%); $\lambda_{max.}$ 250 (ε 12 954) and 289 nm (12 735); $\lambda_{min.}$ 269 nm (ε 10 200) in acidic ethanol; $\lambda_{max.}$ 250 (ε 11 517) and 292 nm (11 956); $\lambda_{min.}$ 269 nm (ε 8 563) in ethanol; $\lambda_{max.}$ 262 (ε 9 182) and 307 nm (14 811); $\lambda_{min.}$ 240 (ε 6 387) and 280 nm (8 503) in alkaline ethanol; δ 7.63, 7.69 (2 H, 2 s, 6-H and vinylic H, precise assignment not made), and 11.36 (2 H, s, NH), *m/e* 254 (1%), 252 (4), 250 (3) (M^+), 217 (4), 215 (4), 173 (54), 171 (100), 128 (7), and 100 (9).

5-Bromoethynyluracil (9).—To a suspension of 5-(2-bromo-1-chlorovinyl)uracil (753 mg) in methanol (30 ml) was added sodium (0.5 g) in small portions. When the exothermic dissolution of sodium had ceased the mixture was shaken for 15 min and then the solvent removed under reduced pressure. The residue was dissolved in water (20 ml) and the solution adjusted to pH 6 by the addition of dilute HCl. The resulting precipitate was filtered off and dried to give 5-*bromoethynyluracil* (9) (592 mg, 92%) (Found: C, 33.5; H, 1.7; Br, 37.5; N, 13.1. $C_6H_3BrN_2O_2$ requires C, 33.5; H, 1.40; Br, 37.2; N, 13.0%); $\lambda_{max.}$ 231 (ε 12 380), and 290 nm (12 750); $\lambda_{min.}$ 256 nm (ε 5 690) at pH 1; $\lambda_{max.}$ 232 (ε 10 910), and 290 nm (12 150) at pH 7; $\lambda_{max.}$ 249 (ε 12 450) and 306 nm (13 940); $\lambda_{min.}$ 276 nm (ε 6 290) at pH 13; δ 7.83 (1 H, s, 6-H) and 11.3 (2 H, br s, NH); δ_C 54.04 ($\equiv$CBr), 72.98 (C$\equiv$), 96.68 (C-5), 147.0 (C-6), 150.5 (C-2), and 162.9 p.p.m. (C-4); *m/e* 217 (100%), 216 (100) (M^+), 215 (100), 214 (88) (M^+), 173 (34), 171 (40), 97 (54), 83 (53), 81 (48), 71 (48), 69 (54), and 57 (56).

Bis(trimethylsilyl) Derivative of (E)-5-(2-*Bromovinyl*)-*uracil.*—A suspension of (*E*)-5-(2-bromovinyl)uracil (3.62 g) in hexamethyldisilazane (15 ml) and trimethylsilyl chloride (0.1 ml) was boiled under reflux for 1 h whereupon a clear solution was obtained. The liquid reagents were removed by distillation under reduced pressure and the residue distilled under high vacuum at 120—130 °C to give the *required bis*(*trimethylsilyl*) *derivative* as a colourless oil (5.04 g, 84%); δ(CCl$_4$) 0.30, 0.38 (18 H, 2 s, Me$_3$Si on 2-O and 4-O), 6.83 (2 H, s, vinylic H), and 8.05 (1 H, s, 6-H).

(E)-5-(2-*Bromovinyl*)-2'-*deoxy*-3',5'-*di*-O-(p-*toluoyl*)*uridine* (10) *and its* α-*Anomer* (18).—The above-mentioned trimethylsilyl derivative (5 g, 14 mmol) was dissolved in dry 1,2-dichloroethane (50 ml) and added to a solution of 2-deoxy-3,5-di-O-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (4 g, 13 mmol) in dry 1,2-dichloroethane (50 ml). The reaction mixture was stirred at *ca.* 20 °C for 8 h and then evaporated to dryness under reduced pressure. The resulting oil was applied to a silica gel column which was eluted with benzene–ethyl acetate (7 : 3) to give a mixture of the α- and β-anomers of the protected nucleoside (5.3 g) (n.m.r. spectroscopy showed that the ratio of α- to β-

anomers was 1.3 : 1). The anomers were separated by column chromatography on silica gel using chloroform–propan-2-ol (99 : 1) as the eluant. The faster-running nucleoside was crystallised from methanol to give (E)-5-(2-*bromovinyl*)-2'-*deoxy*-3',5'-*di*-O-(p-*toluoyl*)*uridine* (10) as colourless crystals, m.p. 186—188 °C (decomp.) (Found: C, 56.6; H, 4.7; N, 4.6. $C_{27}H_{25}BrN_2O_7$ requires C, 56.9; H, 4.43; N, 4.92%); $\lambda_{max.}$ 244 (ε 37 400) and 286sh nm (8 550) in ethanol; δ(CDCl$_3$) 2.42 (6 H, s, Me), 2.7 (2 H, m, 2'-H), 4.54 (1 H, m, 4'-H), 4.72 (2 H, m, 5'-H), 5.62 (1 H, m, 3'-H), 6.08 (1 H, d, *J* 13 Hz, vinylic H), 6.40 (1 H, t, 1'-H), 7.26 (5 H, m, ArH and vinylic H), 7.41 (1 H, s, 6-H), 7.94 (4 H, m, ArH), and 8.28 (1 H, s, NH).

The slower-running nucleoside was crystallised from methanol to give (E)-5-(2-*bromovinyl*)-1-[2-*deoxy*-3,5-*di*-O-(p-*toluoyl*)-α-D-erythro-*pentofuranosyl*]*uracil* (18), m.p. 105 °C (Found: C, 56.6; H, 4.4; Br, 14.0; N, 5.2. $C_{27}H_{25}BrN_2O_7$ requires C, 56.9; H, 4.43; Br, 14.0; N, 4.92%); $\lambda_{max.}$ 243 (ε 42 000) and 296 nm (12 100); $\lambda_{min.}$ 272 nm (ε 9 100) in ethanol; δ(CDCl$_3$) 2.40 (6 H, s, Me), 2.75 (2 H, br m, 2'-H), 4.48 (2 H, m, 5'-H), 4.88 (1 H, t, 4'-H), 5.60 (1 H, m, 3'-H), 6.36 (1 H, d, 1'-H), 6.52 (1 H, d, *J* 13 Hz, vinylic H), 7.23 (5 H, m, ArH and vinylic H), 7.52 (1 H, s, 6-H), 7.82 (4 H, m, ArH), and 9.32 (1 H, s, NH).

(E)-5-(2-*Bromovinyl*)-2'-*deoxyuridine* (11) *and its* α-*Anomer* (19).—(*E*)-5-(2-Bromovinyl)-2'-deoxy-3',5'-di-*O*-(*p*-toluoyl)uridine (920 mg) was dissolved in 0.1M sodium methoxide in methanol (15 ml) and the mixture kept at 22 °C for 24 h. The solution was adjusted to pH 6 by the addition of Dowex 50 ion-exchange resin (H$^+$ form), the resin filtered off, washed with aqueous methanol (50 ml), and the filtrate and washings evaporated to give a white solid. This was triturated with diethyl ether (3 × 10 ml) and the solid dried under reduced pressure to give the crude product (508 mg, 94%). Crystallisation from methanol–water gave pure (E)-5-(2-*bromovinyl*)-2'-*deoxyuridine* (11), m.p. 123—125 °C (decomp.) (Found: C, 40.1; H, 4.2; N, 8.2. $C_{11}H_{13}BrN_2O_5$ requires C, 39.7; H, 3.93; N, 8.41%); $\lambda_{max.}$ 253 (ε 13 100) and 295 nm (10 300); $\lambda_{min.}$ 274 nm (ε 7 500) in ethanol; δ 2.12 (2 H, m, 2'-H), 3.58 (2 H, m, 5'-H), 3.78 (1 H, m, 4'-H), 4.22 (1 H, m, 3'-H), 5.02 (1 H, t, 5'-OH), 5.18 (1 H, d, 3'-OH), 6.10 (1 H, t, 1'-H), 6.81 (1 H, d, *J* 13 Hz, vinylic H), 7.24 (1 H, d, *J* 13 Hz, vinylic H), 8.08 (1 H, s, 6-H), and 11.24 (1 H, s, NH).

Removal of the blocking groups from the α-anomer in a similar way and crystallisation from methanol gave (E)-5-(2-*bromovinyl*)-1-(2-*deoxy*-α-D-erythro-*pentofuranosyl*)-*uracil* (19), m.p. 161—162 °C (decomp.) (Found: C, 39.4; H, 4.1; Br, 23.7; N, 8.3. $C_{11}H_{13}BrN_2O_5$ requires C, 39.7; H, 3.93; Br, 24.0; N, 8.41%); $\lambda_{max.}$ 255 nm (ε 15 800) and 296 nm (12 250); $\lambda_{min.}$ 274 nm (ε 8 900) in ethanol; δ 1.8—2.7 (2 H, br m, 2'-H), 3.41 (2 H, m, 5'-H), 4.24 (2 H, m, 3'- and 4'-H), 4.4—5.3 (2 H, m, 3'- and 5'-OH), 6.05 (1 H, dd, 1'-H), 6.86 (1 H, d, *J* 13 Hz, vinylic H), 7.25 (1 H, d, *J* 13 Hz, vinylic H), 8.03 (1 H, s, 6-H), and 11.34 (1 H, s, NH).

Bis(trimethylsilyl) Derivative of (E)-5-(2-*Iodovinyl*)-*uracil.*—(*E*)-5-(2-Iodovinyl)uracil (1 g) was suspended in hexamethyldisilazane (8 ml) and trimethylsilyl chloride (0.1 ml) added. The solution was boiled under reflux for 1 h whereupon a clear solution was formed. The excess of silylating agent was distilled off under reduced pressure and the residual oil distilled under high vacuum at 130—160 °C to give the required *bis*(*trimethylsilyl*) *derivative* as a yellow oil (554 mg, 36%); δ(CCl$_4$) 0.30, 0.40 (18 H, 2 s, Me$_3$Si on

2-O and 4-O), 6.80 (1 H, d, J 15 Hz, vinylic H), 7.20 (1 H, d, J 15 Hz, vinylic H), and 8.00 (1 H, s, 6-H).

(E)-2'-*Deoxy*-5-(2-*iodovinyl*)*uridine* (12).—Condensation of the above-mentioned trimethylsilyl derivative (500 mg) with 2-deoxy-3,5-di-O-(p-toluoyl)-α-D-*erythro*-pentofurano-syl chloride was carried out in a similar manner to the procedure used for the bromovinyl derivative. The α- and β-anomers were separated by chromatography on silica gel in benzene–ethyl acetate (4 : 1). The faster-running nucleoside was crystallised from methanol to give the protected β-nucleoside, $\lambda_{max.}$ 242 (ε 33 950) and 295 nm (9 650); $\lambda_{min.}$ 272 nm (ε 7 850) in ethanol). The p-toluoyl protecting groups were removed in the usual way to give (E)-2'-*deoxy*-5-(2-*iodovinyl*)*uridine* (12) (22 mg) (Found: C, 33.1; H, 3.3; N, 7.1. $C_{11}H_{13}IN_2O_5 \cdot H_2O$ requires C, 33.2; H, 3.80; N, 7.04%); $\lambda_{max.}$ 250 (ε 14 100), and 295 nm (11 450); $\lambda_{min.}$ 275 nm (ε 8 450) in ethanol; δ 2.02 (2 H, m, 2'-H), 3.60 (2 H, m, 5'-H), 3.78 (1 H, m, 4'-H), 4.23 (1 H, m, 3'-H), 5.03 (1 H, m, 5'-OH), 5.19 (1 H, d, 3'-OH), 6.11 (1 H, t, 1'-H), 7.14 (2 H, s, vinylic H), 8.05 (1 H, s, 6-H), and 11.48 (1 H, br s, NH); δ(CD₃OD) 2.19 (2 H, m, 2'-H), 3.72 (2 H, m, 5'-H), 3.85 (1 H, m, 4'-H), 4.32 (1 H, m, 3'-H), 6.16 (1 H, t, 1'-H), 7.00 (1 H, d, J 15 Hz, vinylic H), 7.20 (1 H, d, J 15 Hz, vinylic H), and 8.04 (1 H, s, 6-H).

The α-anomer of the protected nucleoside was also isolated and identified by n.m.r. spectroscopy, but it was not completely characterised.

5-(2-*Bromo*-1-*chlorovinyl*)-2'-*deoxy*-3',5'-*di*-O-(p-*toluoyl*)-*uridine* (13).—A suspension of 5-(2-bromo-1-chlorovinyl)-uracil (3.24 g) in hexamethyldisilazane (30 ml) and trime-thylsilyl chloride (0.25 ml) was boiled under reflux for 20 h. The hexamethyldisilazane was removed by evaporation under reduced pressure and the residue distilled under high vacuum to give the trimethylsilyl derivative as a colourless oil (4.7 g, 92%). This was dissolved in dry 1,2-dichloro-ethane (20 ml) and added to a solution of 2-deoxy-3,5-di-O-(p-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (4.6 g) and mercury(II) bromide (43 mg) in 1,2-dichloroethane (150 ml). The mixture was stirred at room temperature for 50 h and then evaporated under reduced pressure to give a white foam. This was crystallised from ethanol–chloroform (4 : 1) to give 5-(2-*bromo*-1-*chlorovinyl*)-2'-*deoxy*-3',5'-*di*-O-(p-*toluoyl*)*uridine* (2.46 g) (13). After re-crystallisation from methanol–chloroform the product had m.p. 218—220 °C (Found: C, 53.8; H, 4.2; N, 4.7. C_{27}-$H_{24}BrClN_2O_7$ requires C, 53.7; H, 4.00; N, 4.64%); $\lambda_{max.}$ 243 (ε 42 547) and 294 nm (ε 13 036); $\lambda_{min.}$ 271 nm (ε 10 561) in ethanol; δ 2.30 (6 H, s, Me), 2.66 (2 H, m, 2'-H), 4.58 (3 H, m, 4'- and 5'-H), 5.60 (1 H, m, 3'-H), 6.25 (1 H, t, 1'-H), 7.28, 7.34, 7.84, 7.92 (8 H, 4 d, ArH), 7.62 (1 H, s, vinylic H), 8.01 (1 H, s, 6-H), and 11.8 (1 H, s, NH). The mother liquor contained the α-anomer, which was not completely characterised.

5-(2-*Bromo*-1-*chlorovinyl*)-2'-*deoxyuridine* (14).—To a suspension of the aforementioned β-anomer (907 mg) in dry methanol (100 ml) was added sodium (172 mg) in small portions. After the sodium had dissolved the mixture was shaken at room temperature until a clear solution was obtained (45 min). It was then adjusted to pH 6 by the addition of Dowex 50 ion-exchange resin (H⁺ form), the resin was filtered off, and washed, and the filtrate and wash-ings were evaporated to dryness to give a white solid. This was triturated with ether (3 × 5 ml) and the residue crystallised from methanol–water to give 5-(2-*bromo*-1-*chlorovinyl*)-2'-*deoxyuridine* (14) (430 mg, 78%), m.p.

162—164 °C (Found: C, 36.2; H, 3.3; N, 7.3. $C_{11}H_{12}$-$BrClN_2O_5$ requires C, 35.9; H, 3.29; N, 7.62%); $\lambda_{max.}$ 250 (ε 11 944) and 294 nm (ε 14 264); $\lambda_{min.}$ 268 nm (ε 9 348) in ethanol; δ 2.18 (2 H, m, 2'-H), 3.62 (2 H, m, 5'-H), 3.84 (1 H, m, 4'-H), 4.24 (1 H, m, 3'-H), 5.02 (1 H, br s, 5'-OH), 5.20 (1 H, br s, 3'-OH), 6.16 (1 H, t, 1'-H), 8.42 (1 H, s, 6-H), 8.66 (1 H, s, vinylic H), and 11.0 (1 H, br s, NH).

Trimethylsilyl Derivative of 5-(1-*Chlorovinyl*)*uracil*.—5-(1-Chlorovinyl)uracil (2.2 g) was suspended in hexamethyl-disilazane (15 ml) and trimethylsilyl chloride (0.1 ml) added. The suspension was boiled under reflux for 12 h whereupon a clear solution was obtained. The excess of silylating agent was removed by distillation under reduced pressure and the residual oil distilled under high vacuum at 120—130 °C to give the required *bis*(*trimethylsilyl*) *derivative* as a colourless oil (3.92 g, 97%); δ(CCl₄) 0.31, 0.37 (18 H, 2, Me₃Si on 2-O and 4-O), 5.66 (1 H, d, J 1 Hz, vinylic H), 6.02 (1 H, d, J 1 Hz, vinylic H), and 8.69 (1 H, s, 6-H).

5-(1-*Chlorovinyl*)-2'-*deoxy*-3',5'-*di*-O-(p-*toluoyl*)*uridine* (15).—The aforementioned trimethylsilyl derivative (1.3 g) was dissolved in dry 1,2-dichloroethane (5 ml) and added to a solution of 2-deoxy-3,5-di-O-(p-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (1.4 g) and mercury(II) bromide (13 mg) in dry 1,2-dichloroethane (20 ml). The reaction mixture was stirred at room temperature for 20 h and then evaporated to dryness under reduced pressure. The result-ing oil was applied to a silica-gel column which was eluted with benzene–ethyl acetate (7 : 3). This procedure purified the blocked nucleosides and separated the α- and β-anomers. The faster-running blocked nucleoside was crystallised from methanol to give 5-(1-*chlorovinyl*)-2'-*deoxy*-3',5'-*di*-O-(p-*toluoyl*)*uridine* (15) (620 mg, 33%), m.p. 187—189 °C (decomp.) (Found: C, 62.1; H, 4.7; Cl, 6.6; N, 5.2. $C_{27}H_{25}ClN_2O_7$ requires C, 61.8; H, 4.80; Cl, 6.75; N, 5.34%); $\lambda_{max.}$ 244 (ε 34 860) and 286 nm (11 820); $\lambda_{min.}$ 267 nm (ε 8 960) in ethanol; δ(CDCl₃) 2.36, 2.39 (6 H, 2 s, Me), 2.75 (2 H, m, 2'-H), 4.65 (3 H, m, 4' and 5'-H), 5.50 (1 H, d, J 1.5 Hz, vinylic H), 5.62 (1 H, m, 3'-H), 6.38 (1 H, t, 1'-H), 6.50 (1 H, d, J 1.5 Hz, vinylic H), 7.20 (4 H, m, ArH), 7.91 (4 H, m, ArH), 8.08 (1 H, s, 6-H), and 9.54 (1 H, s, NH). The α-anomer was also obtained (26% yield), but it was not completely characterised.

The Action of Methanolic Ammonia on 5-(1-*Chlorovinyl*)-2'-*deoxy*-3',5'-*di*-O-(p-*toluoyl*)*uridine*.—A solution of this compound (550 mg) in methanol saturated with ammonia at 0 °C (100 ml) was allowed to stand at *ca.* 20 °C for 2 d [t.l.c. in chloroform–ethanol (9 : 1) showed the absence of starting material and the presence of two products]. The reaction mixture was evaporated to dryness and the solid residue fractionated by chromatography on silica gel. The nucleoside products were obtained by elution with chloro-form–ethanol (9 : 1). The faster-running nucleoside was crystallised from ethanol–water (19 : 1) to give 2'-*deoxy*-5-*ethynyl*-5'-O-(p-*toluoyl*)*uridine* (21) as its monohydrate (50 mg, 12%), m.p. 117—118 °C (Found: C, 58.8; H, 5.6; N, 7.2. $C_{19}H_{18}N_2O_6 \cdot H_2O$ requires C, 58.8; H, 5.19; N, 7.22%); $\lambda_{max.}$ 239 (ε 20 400) and 287 nm (12 900); $\lambda_{min.}$ 262 nm (ε 6 100) in ethanol; δ 2.38 (3 H, s, Me), 3.26 (s, H₂O), 4.00 (1 H, s, ≡CH), 4.44 (2 H, m, 5'-H), 5.42 (1 H, br s, 3'-OH), 6.11 (1 H, t, 1-H), 7.30 (2 H, m, ArH), 7.88 (3 H, m, 6-H and ArH), and 11.50 (1 H, br s, NH).

The slower-running nucleoside was isolated and identified as 2'-deoxy-5-ethynyluridine (20) (123 mg, 47% yield) by comparison with an authentic specimen.[18]

5-(1-*Chlorovinyl*)-2'-*deoxyuridine* (16).—2'-Deoxy-5-ethynyluridine (200 mg) was suspended in 2M HCl and the suspension evaporated to dryness at 40 °C under reduced pressure. To the residue was added 2M HCl (10 ml) and the mixture was again evaporated to dryness at 40 °C. The white solid thus formed was stored *in vacuo* over soda-lime for 18 h. N.m.r. spectroscopy showed that this solid contained a mixture of the required product and 5-acetyl-2'-deoxyuridine. Crystallisation of this mixture from methanol–water gave 5-(1-*chlorovinyl*)-2'-*deoxyuridine* (16) (150 mg, 65%), m.p. 108—110 °C (decomp.) (Found: C, 45.8; H, 4.8; N, 9.9. $C_{11}H_{13}ClN_2O_5$ requires C, 45.8; H, 4.54; N, 9.70%); $\lambda_{max.}$ 234 (ε 9 370) and 282 nm (10 500); $\lambda_{min.}$ 259 nm (ε 6 650) at pH 6; δ 2.17 (2 H, m, 2'-H), 3.70 (2 H, m, 5'-H), 3.86 (1 H, m, 4'-H), 4.25 (1 H, m, 3'-H), 5.10 (2 H, br s, 3' and 5'-OH), 5.54 (1 H, s, vinylic H), 6.18 (1 H, t, 1'-H), 6.43 (1 H, s, vinylic H), 8.37 (1 H, s, 6-H), and 11.2 (1 H, s, NH).

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