Tetrahedron. Vol. 26, pp. 1023 to 1030. Pergamon Press 1970. Printed in Great Britain

4-METHOXYTETRAHYDROPYRAN-4-YL
A SYMMETRICAL ALTERNATIVE TO THE TETRAHYDROPYRANYL PROTECTING GROUP*

C. B. REESE, R. SAFFHILL and J. E. SULSTON

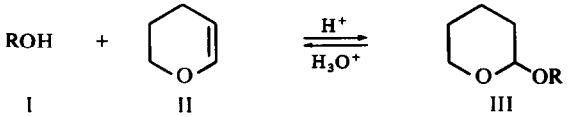
University Chemical Laboratory, Cambridge, England

Received in UK 2 *September* 1969; *Accepted for publication* 3 *October* 1969

Abstract—The possibility of using a symmetrical ketal function as an alternative to the tetrahydropyranyl protecting group has been examined. Although simple ketal functions (derived from acetone and cyclohexanone) appear to be too labile to acidic hydrolysis to be useful as protecting groups, ketals of tetrahydro-4*H*-pyran-4-one have the desired hydrolysis properties.

The preparation of 4-methoxy-5,6-dihydro-2*H*-pyran is described; this reagent undergoes rapid acid-catalyzed addition to alcoholic OH functions to give tetrahydro-4*H*-pyran-4-one ketals (methoxytetrahydropyranyl derivatives). The preparations of 2'-O-methoxytetrahydropyranyl-uridine and -adenosine, and of 5'-O-methoxytetrahydropyranyl-thymidine are described; these derivatives have been obtained crystalline, in good yields.

SINCE its introduction by Parham and Anderson[1] over twenty years ago, the tetrahydropyranyl group has found considerable use in the protection of alcoholic OH functions.† Tetrahydropyranyl derivatives (III) may generally be prepared by allowing the alcohol (I) to react with 2,3-dihydro-4*H*-pyran (II), under anhydrous conditions in the presence of acid (Chart 1).



I II III

Chart 1

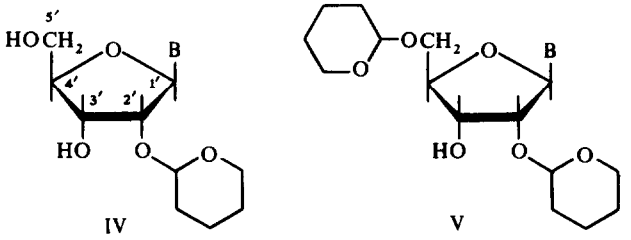
The tetrahydropyranyl function, which is essentially part of an acetal system, is a useful protecting group inasmuch as it is stable in alkaline and neutral media, but labile even under mild conditions of acidic hydrolysis (see below). However, it is not especially suitable for the protection of optically-active alcohols as, due to its lack of symmetry, its use then leads to mixtures of diastereoisomeric products.[2] Such mixtures were first observed in the steroid field[3] and, more recently, diastereoisomeric tetrahydropyranyl derivatives of sugars[4] and nucleosides[5] have been obtained.

We encountered this complication in the nucleoside field when, in connection with our work on oligoribonucleotide synthesis,[6] we set out to obtain pure crystalline 2'-O-tetrahydropyranyl- and 2',5'-di-O-tetrahydropyranyl-derivatives of ribonucleosides (IV and V, respectively). Although we succeeded in isolating monoacetals (such

* For a preliminary account of this work, see C. B. Reese, R. Saffhill and J. E. Sulston, *J. Am. Chem. Soc.* **89**, 3366 (1967).

† For reviews, see reference 2 and J. F. W. McOmie in *Advances in Organic Chemistry: Methods and Results* Vol 3, p. 218. Interscience, New York (1963).

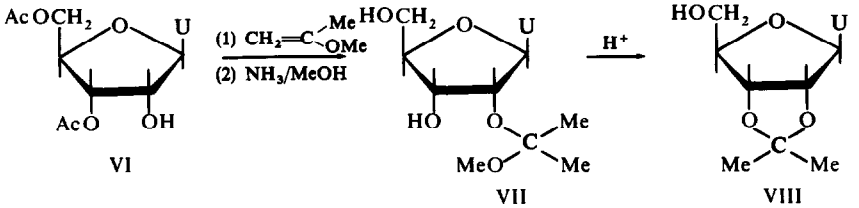
as IVa and IVb) in a pure crystalline state, we generally obtained approximately equal quantities of both diastereoisomers.[5] Thus a fairly laborious fractionation process was necessary, and the yield of either pure compound never exceeded ca. 50%. The situation with bisacetals (such as V) was even less promising in that mixtures of four diastereoisomers were likely to be obtained. In the case of 2',5'-di-O-tetrahydropyranyluridine[7] (Va), the mixture of diastereoisomers was resolved into three components by TLC. Attempts to isolate one diastereoisomer, in a pure crystalline state, were unsuccessful.



IV V

a: B = uracil-1
b: B = adenine-9

In that it has satisfactory hydrolysis properties,[5] the tetrahydropyranyl group is otherwise suitable for the protection of the 2'-OH functions of the ribose moieties in an oligoribonucleotide synthesis. Therefore in order to avoid the above complication, it seemed desirable to find a symmetrical protecting group with similar hydrolysis properties. An appreciably more labile (to acidic hydrolysis) group was unlikely to be of much practical value, whereas an appreciably more stable group was likely to be unsatisfactory in that its removal would lead to undesirable side-reactions.[5] Perhaps the most obvious solution to the present problem was to use a symmetrical ketal system instead of the tetrahydropyranyl protecting group. However, the kinetic data of Kreevoy and Taft[8] suggested that the rate of hydrolysis of a simple ketal would be ca. 10^3 times as fast* as that of the corresponding tetrahydropyranyl derivative. This was indeed found to be the case.



VI VII VIII

U = uracil-1

Reaction between 3',5'-di-O-acetyluridine[9] (VI) and 2-methoxypropene in the presence of toluene-*p*-sulphonic acid, followed by treatment with methanolic ammonia gave the uridine 2'-ketal (VII), which was isolated crystalline in 42% overall yield. The latter compound was extremely sensitive to aqueous acid; in pH 4

* These kinetic data[8] also suggested that the rate of hydrolysis of a formaldehyde acetal would be ca. 10^3 times as slow as that of the corresponding tetrahydropyranyl derivative.

buffer solution at 20°, it had $t_{\frac{1}{2}}$ = 4·1 min (Table 1). As the rate of ketal hydrolsis[8] is proportional to $[H^+]$, $t_{\frac{1}{2}}$ would be expected to be ca. 0·04 min at pH 2 and 20°. Thus the rate of hydrolysis of the uridine 2'-ketal (VII) was estimated to be nearly 2000 times

TABLE 1. ACID-CATALYZED HYDROLYSIS OF NUCLEOSIDE KETALS AT 20°.

Nucleoside derivative	pH	$t_{\frac{1}{2}}$ (min)[a]
2'-O-(1"-Methoxy-1"-methyl)-ethyluridine (VII)	4[b]	4·1
2'-O-(1"-Methoxy)-cyclohexyluridine (XIV)	4[b]	10
2'-O-Methoxytetrahydropyranyluridine (XXa)	2[c]	24
5'-O-Methoxytetrahydropyranylthymidine (XXI)	2[c]	10·5

[a] The rates of hydrolysis were measured at constant pH, and pseudo-first-order kinetics were observed in all cases.
[b] 0·1 M sodium citrate buffer (pH 4·0).
[c] 0·01 N HCl.

as fast as that of 2'-O-tetrahydropyranyluridine (IVa) ($t_{\frac{1}{2}}$ = 67 min in 0·01 N-HCl at 22°).[5] It therefore seemed improbable that the simple acetone ketal system would be stable enough to be generally useful as a protecting group. It is interesting to note that the cyclic acetone ketal, 2',3'-O-isopropylideneuridine[10] (VIII) is ca. 3 × 10^4 times more stable to acidic hydrolysis than the corresponding acyclic ketal (VII). The particular stability of the 1,3-dioxalan system is illustrated by the ready acid-catalyzed conversion* of VII into VIII, in anhydrous dioxan solution.

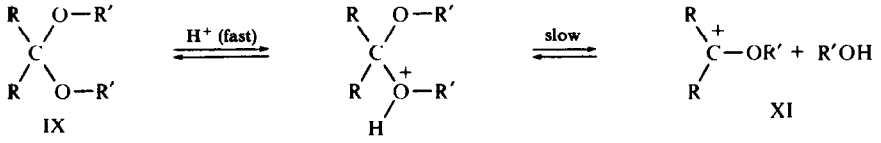


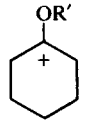
CHART 2

A study of the mechanism of acetal and ketal hydrolysis has revealed that it is a specific acid-catalyzed reaction.[8] The accepted mechanism involves a fast protonation step, followed by the rate-determining decomposition of the conjugate acid (X, chart 2) to give a carbonium (oxonium) ion intermediate[11] (XI), which then undergoes hydrolysis. The overall rate of hydrolysis is therefore dependent on the stability of the intermediate carbonium ion (XI). It was thus clear that a symmetrical ketal protecting group, which would give rise to an intermediate carbonium ion less stable than XI (R=Me), was required.

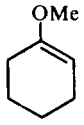
Brown *et al.* have demonstrated[12] the particular electrophilic reactivity of cyclohexanone compared with acyclic and other cyclic ketones. If it were especially unfavourable for an sp^2-hybridized C atom to be located in a 6-membered ring, the

* The most convenient preparation of 2',3'-O-isopropylidene derivatives (such as VIII) involves acid-catalysed ketal-exchange between the appropriate ribonucleoside and 2,2-dimethoxypropane (A. Hampton, *J. Am. Chem. Soc.* **83**, 3640 (1961); S. Chládek and J. Smrt, *Coll. Czech. Chem. Commun.* **28**, 1301 (1963); H. P. M. Fromageot, B. E. Griffin, C. B. Reese and J. E. Sulston, *Tetrahedron* **23**, 2315 (1967)). It seems very likely that acyclic ketals such as VII and its 3'-isomer are intermediates in this reaction and that its facility depends on the particular stability of the cyclic ketal system.

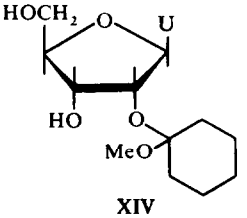
carbonium ion intermediate (XII) derived from a cyclohexanone ketal was likely to be less stable than the intermediate (XI; R=Me) derived from the corresponding acetone ketal. Reaction between 1-methoxycyclohexene[13] (XIII) and 3',5'-di-O-acetyluridine[9]



XII

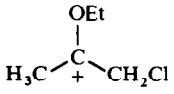


XIII

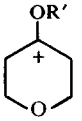


XIV

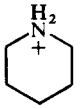
(VI), followed by ammonolysis, gave the desired cyclohexanone ketal (XIV). Unfortunately, the latter compound was only 2–3 times more stable (Table 1) to acidic hydrolysis than the corresponding acetone ketal (VII), and therefore the cyclohexanone ketal system was also unlikely to be useful as a protecting group.



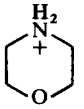
XV



XVI



XVII



XVIII

Kreevoy and Taft have shown[8] that acetal and ketal systems can be stabilized to acidic hydrolysis by the introduction of electron-withdrawing groups. Thus the diethyl ketal of acetone was found[8] to undergo hydrolysis at a rate $8{\cdot}75 \times 10^3$ times as fast as that of the corresponding ketal of chloroacetone. This is in accord with the above mechanism as the carbonium ion (XI; R=Me, R'=Et) derived from the acetone ketal would be expected to be more stable than XV. It was therefore anticipated that if the 4—CH_2 group of XII were replaced by an ether grouping, a less stable carbonium ion (XVI) would be obtained. In the case of the corresponding ammonium ions (piperidinium XVII and morpholinium XVIII), it can be estimated from *pKa* data,* that a similar replacement of —CH_2— by —O— leads to a lowering of stability by a factor of $10^{2{\cdot}52}$ or 330. Although, due to hybridization and other differences, it cannot be expected that the relative stabilities of the carbonium ions (XII and XVI) and the ammonium ions (XVII and XVIII) would be precisely the same, it seemed reasonable that there should be a qualitative correspondence. If second order kinetics are assumed, the half-time of hydrolysis of XIV (Table 1) would be 0·1 min at pH 2 and 20°, and thus 2'-O-methoxytetrahydropyranyluridine‡ (XXa) should have $t_{\frac{1}{2}} \sim 33$ min under the same conditions.

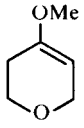
The required enol ether, 4-methoxy-5,6-dihydro-2*H*-pyran (XIX) was prepared by heating tetrahydro-4*H*-pyran-4-one[14] dimethyl ketal with a trace of mesitylenesulphonic acid.‡ Acid-catalyzed reaction between 3',5'-di-O-acetyluridine[9] (VI) and

* The *pKa*'s of piperidine and morpholine are 11·22 and 8·70, respectively [A. Albert and E. P. Serjeant, *Ionization Constants of Acids and Bases* p. 141. Methuen, London (1962)].

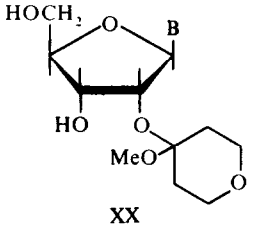
† Methoxytetrahydropyranyl is an abbreviation for 4-Methoxytetrahydropyran-4-yl.

‡ The material prepared in this way was generally ca. 90% pure; it was contaminated both with the corresponding ketone and dimethyl ketal. However, these impurities do not lead to side-reactions.

an excess of XIX, followed by ammonolysis, gave 2′-O-methoxytetrahydropyranyluridine (XXa), which was isolated as a colourless crystalline solid in 82% overall yield. In the same way, 2′-O-methoxytetrahydropyranyladenosine (XXb) and 5′-O-methoxytetrahydropyranylthymidine (XXI) were prepared from 3′,5′-di-O-acetyladenosine[9] and 3′-O-acetylthymidine,[15] respectively. Both compounds were isolated in the crystalline state; their respective overall yields were 73 and 85%. Thus the use of this symmetrical protecting group appears to lead to very satisfactory yields of pure crystalline derivatives.

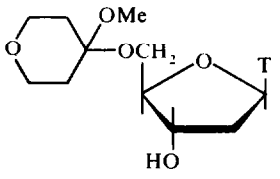


XIX



XX

a: B = uracil-1
b: B = adenine-9



XXI: T = thymine-1

2′-O-Methoxytetrahydropyranyluridine (XXa) was found to have $t_{\frac{1}{2}} = 24$ min in 0·01 N HCl at 20° (Table 1). Thus the experimental half-time of hydrolysis was surprisingly close to the above estimate (33 min), and was ca. one-third that of 2′-O-tetrahydropyranyluridine[5] (IVa) under the same conditions (see above). 2′-O-Methoxytetrahydropyranyladenosine (XXb) underwent hydrolysis at the same rate as that of the uridine derivative (XXa), but hydrolysis of the 5′-ketal function in the thymidine derivative (XXI) occurred more rapidly (Table 1).

The methoxytetrahydropyranyl protecting group appears to represent a satisfactory solution to the present problem; it is symmetrical and may be removed by acid-catalyzed hydrolysis at a rate which is comparable with that of the tetrahydropyranyl group. The advantage in using the symmetrical group to protect optically-active alcohols is clearly illustrated by the good yields of crystalline ribonucleoside derivatives which may then be obtained (see above). This advantage will become even more apparent in the following paper,[16] which is concerned with the preparation of ribonucleoside 2′,5′-bisketals.

EXPERIMENTAL

UV absorption spectra were measured with a Cary recording spectrophotometer, model 14M-50. NMR spectra were measured with a Perkin–Elmer spectrometer, operating at 60 MHz, with Me_4Si as internal standard.

Unless otherwise stated, paper chromatography was run on Whatman No. 1 paper in solvent system A [propan-2-ol-ammonia (*d.* 0·88)-water (7:1:2)]. Plates coated with Merck Kieselgel GF_{254} were used for TLC, and the chromatograms were developed with solutions of MeOH in $CHCl_3$. Mallinckrodt analytical grade silicic acid and SilicAR CC7 were used for adsorption chromatography. Dioxan was dried by heating under reflux, first with CaH_2 and then with LAH; it was finally redistilled.

2-Methoxypropene

2,2-Dimethoxypropane (80 g) and toluene-*p*-sulphonic acid, monohydrate (0·2 g) were heated together in a fractional distillation apparatus, fitted with a column of glass helices. The fraction with b.p. 50° was collected and redistilled in the same apparatus to give 2-methoxypropene (35 g, 63%), b.p. 34–36° (lit.[17] 38°).

2'-O-(1''-Methoxy-1''-methyl)-ethyluridine (VII)

2-Methoxypropene (0·76 g, 10·6 mmole) was added to a soln of VI (0·5 g, 1·52 mmole) and toluene-*p*-sulphonic acid, monohydrate (0·006 g, 0·03 mmole) in anhyd dioxan (5 ml). The reactants were stirred at 20° for 10 min and then carefully neutralized with NaOMe/MeOH. After the evaporation of the solvents, the residue was redissolved in NH_3/MeOH (10 ml; half-saturated at 0°) and the soln allowed to stand at 20° for 14 hr. Evaporation of the solvent gave a TLC homogeneous material which was recrystallized from abs EtOH. The 2'-O-(1''-*methoxy*-1''-*methyl*)-*ethyluridine* (0·20 g, 42%), so obtained, was further purified by preparative TLC [solvent system: $CHCl_3$–MeOH (9:1, v/v)] to give an analytical specimen [Found: C, 49·2; H, 6·5; N, 9·0. $C_{13}H_{20}N_2O_7$ requires: C, 49·4; H, 6·4; N, 8·9%] with m.p. 185° dec; UV absorption (95% EtOH): λ_{max}260 (ε 10,200), λ_{min} 230 nm (ε 3,500); R_f: 0·59 (system A).

Cyclization of 2'-O-(1''-methoxy-1''-methyl)-ethyluridine (VII)

2'-O-(1''-Methoxy-1''-methyl)-ethyluridine (0·05 g) was added to a soln of toluene-*p*-sulphonic acid, monohydrate (0·005 g) in anhyd dioxan (1 ml) which had first been stirred with 4A molecular sieves (0·05 g) at 20° for 15 min. After 5 min, the reactants were neutralized with NaOMe/MeOH and the solvents evaporated. The residue was fractionated by preparative TLC. [solvent system: $CHCl_3$–MeOH (92:8)]. The major (more mobile) component was eluted with MeOH; it had m.p. 162–164° and was identified (mixed m.p., paper chromatography and TLC) as VIII. (Found: C, 50·8; H, 5·9; N, 9·9. Calc. for $C_{12}H_{16}N_2O_6$: C, 50·7; H, 5·7; N, 9·9%), yield, 0·03 g (67%).

2'-O-(1''-Methoxy)-cyclohexyluridine (XIV)

1-Methoxycyclohexene[13] (1·5 g, 13 mmole) was added to a soln of VI[9] (0·5 g, 1·52 mmole) and toluene-*p*-sulphonic acid, monohydrate (0·05 g, 0·26 mmole) in anhyd dioxan (8 ml). After the reactants had been stirred for 10 hr at 20°, TLC indicated that only 50% of the starting material remained. The reaction soln was then neutralized with NaOMe/MeOH, the solvents evaporated, and the residue dissolved in NH_3/MeOH (10 ml; half-saturated at 0°) at 20°. After 12 hr, the products were evaporated, the residue redissolved in $CHCl_3$ and applied to a column (11 cm × 2 cm^2) of neutral alumina (grade III). The desired 2'-O-(1''-*methoxy*)-*cyclohexyluridine*, which was eluted with $CHCl_3$–MeOH (96:4) crystallized from EtOAc; yield 0·16 g (30%). An analytical specimen (Found: C, 54·0; H, 6·5; N, 7·8. $C_{16}H_{24}N_2O_7$ requires: C, 53·9; H, 6·8; N, 7·9%), obtained after several recrystallizations from EtOAc, had m.p. 149–151°; UV absorption (95% EtOH): λ_{max}262 (ε 9600), λ_{min} 229 nm (ε 1900); R_f 0·70 (system A).

4,4-Dimethoxytetrahydro-4H-pyran

Tetrahydro-4*H*-pyran-4-one[14] (175 g, 1·75 mole), trimethyl orthoformate (238 ml, 2·18 mole), abs MeOH (300 ml) and mesitylenesulphonic acid (1·0 g, 0·005 mole) were heated together, under reflux, for 15 min. The products were cooled, neutralized with M–NaOMe/MeOH (ca. 5 ml), and distilled to give 4,4-*dimethoxytetrahydro*-4H-*pyran* (Found: C, 57·7; H, 9·9. $C_7H_{14}O_3$ requires: C, 57·6; H, 9·6%), b.p. 64–66°/15 mm; yield, 246 g (94%); NMR spectrum (CCl_4): τ 6·43 (t, J = 5·5 Hz), 4H; τ 6·87 (s), 6H; τ 8·35 (t, J = 5·5 Hz), 4H.

4-Methoxy-5,6-dihydro-2H-pyran (XIX)

A mixture of 4,4-dimethoxytetrahydro-4*H*-pyran (28 g, 0·169 mole) and mesitylenesulphonic acid (0·03 g, 0·15 mmole), contained in a distillation apparatus, was heated (bath temp, 160°) under atm press. When the theoretical amount (ca. 7 ml) of MeOH had been collected, the residue was distilled under reduced press (water-pump) to give the desired product (17 g, 78%); b.p. 56–58°/14 mm (156–157°/760 mm). Redistillation from a trace of NaOMe gave material which was 90–95% pure. Further fractionation by preparative GLC gave pure 4-*methoxy*-5,6-*dihydro*-2H-*pyran* (Found: C, 62·7; H, 9·4. $C_6H_{10}O_2$ requires: C, 63·2; H, 8·8%); ν_{max} 1675 cm^{-1}; NMR spectrum (CCl_4): τ 5·48 (m), 1H; τ 5·90 (m), 2H; τ 6·26 (t), 2H; τ 6·50 (s), 3H; τ 7·90 (m), 2H.

4-Methoxy-5,6-dihydro-2*H*-pyran has a tendency to polymerize, and is best kept in the presence of a trace of alkali.

2'-O-Methoxytetrahydropyranyluridine (XXa)

Compound XIX (3·1 g, 27 mmole) was added to a stirred soln of VI[9] (1·0 g, 3·05 mmole) and toluene-*p*-sulphonic acid, monohydrate (0·045 g, 0·24 mmole) in anhyd dioxan (15 ml) at 20°. After 20 min, when TLC indicated that no starting material remained, the products were neutralized with NaOMe/MeOH and concentrated to a gum. The latter was extracted with $CHCl_3$, the extract filtered through hyflo-supercel,

evaporated and redissolved in NH_3/MeOH (15 ml; half-saturated at 0°). After 16 hr at 20°, the soln was concentrated, redissolved in $CHCl_3$ and applied to a column of silicic acid (10 g) which was then washed with $CHCl_3$.

The fractions containing the desired product were eluted from the column with $CHCl_3$–MeOH (98:2); concentration of these fractions and recrystallization from EtOAc gave 2'-O-*methoxytetrahydropyranyluridine* (Found: C, 50·0; H, 5·9; N, 8·1. $C_{15}H_{22}N_2O_8$ requires: C, 50·3; H, 6·1; N, 7·8%) as colourless crystals (0·90 g, 82%), m.p. 167–169°; UV absorption (95% EtOH): λ_{max} 263 (ε 8940), λ_{min} 230 nm (ε 2100); $[\alpha]_D^{23}$ −15·7° (*c* 2, in EtOH); R_f: 0·24 [$CHCl_3$–MeOH (9:1)].

2'-O-*Methoxytetrahydropyranyladenosine* (XXb)

Compound XIX (4·1 g, 36 mmole) was added to a stirred soln of 3',5'-di-O-acetyladenosine[9] (1·0 g, 2·85 mmole) and toluene-*p*-sulphonic acid, monohydrate (0·58 g, 3·05 mmole) in anhyd dioxan (15 ml). After 10 min, when TLC indicated that no starting material remained the products were neutralized with NaOMe/MeOH and concentrated to a gum. The latter was extracted with $CHCl_3$, the extract filtered through hyflo-supercel, evaporated, redissolved in CH_2Cl_2 and applied to a column of neutral alumina (grade III, 50 g). The column was first washed with CH_2Cl_2, and the desired material eluted with $CHCl_3$. The latter $CHCl_3$ eluate was concentrated to a glass, which was dissolved in NH_3/MeOH (15 ml; half-saturated at 0°). After this soln had stood at 20° for 16 hr it was evaporated to a glass, which crystallised from EtOAc to give 2'-O-*Methoxytetrahydropyranyladenosine* (Found: C, 50·2; H, 6·0; N, 18·3. $C_{16}H_{23}N_5O_6$ requires: C, 50·4; H, 6·0; N, 18·4%) as colourless crystals (0·79 g, 73%), m.p. 118–120°; UV absorption (95% EtOH): λ_{max} 260 (ε 14,600), λ_{min} 229 nm (ε 2930); R_f: 0·29 [$CHCl_3$–MeOH (9:1)].

5'-O-*Methoxytetrahydropyranylthymidine* (XXI)

Compound XIX (1 g, 9 mmole) was added to a stirred soln of 3'-O-acetylthymidine[15] (0·3 g, 1·06 mmole) and toluene-*p*-sulphonic acid, monohydrate (0·015 g, 0·08 mmole) in anhyd dioxan (5 ml) at 20°. After 5 min, when TLC indicated that no starting material remained, the products were neutralized with NaOMe/MeOH and concentrated to a gum. The latter was extracted with $CHCl_3$, the extract filtered through hyflo-supercel, evaporated, and redissolved in NH_3/MeOH (half-saturated at 0°). After 16 hr at 20°, the products were concentrated, the residue dissolved in EtOH and re-evaporated. When the latter process had been repeated several times, the material obtained was crystallized from EtOAc to give 5'-O-*Methoxytetrahydropyranylthymidine* (Found: C, 53·8; H, 6·9; N, 7·7. $C_{16}H_{24}N_2O_7$ requires: C, 54·0; H, 6·7; N, 7·9%) as colourless crystals (0·32 g, 85%), m.p. 169–171°; UV absorption (95% EtOH): λ_{max} 267 (ε 9500), λ_{min} 235 nm (ε 1630); $[\alpha]_D^{23}$ + 9·7° (*c* 2, in EtOH); R_f: 0·43 [$CHCl_3$–MeOH (9:1)].

Determination of rates of acid-catalyzed hydrolysis of nucleoside ketals

(*a*) *Acetone and cyclohexanone ketals of uridine.* Samples (0·5 ml) of a 0·02 M soln of substrate in 0·1 M sodium citrate buffer (pH 4) at 20° were removed after suitable intervals of time and added to N aqueous NH_3 (0·1 ml). The basified products (0·025 ml) were applied to a Whatman No. 42 paper chromatogram, which was then developed in system A (ascending). Equal areas of chromatogram containing the spots corresponding to uridine and unchanged ketal, and a blank were cut out and allowed to soak in 0·1 N HCl (6 ml) at 20° for 24 hr. The optical densities (OD's) of both eluates were measured against the blank at λ_{max}.

Straight lines were obtained by plotting $\log_{10}$ [$OD_{uridine}$ + $OD_{ketal}/OD_{uridine}$] against time. The half-times ($t_{\frac{1}{2}}$) of hydrolysis of the acetone and cyclohexanone ketals were found to be 4·1 and 10 min, respectively.

(*b*) 2'-O-*Methoxytetrahydropyranyluridine and* 5'-O-*methoxytetrahydropyranylthymidine.* After suitable intervals of time, samples (0·2 ml) were removed from a soln of substrate (0·030 g, 0·084 mmole) in 0·01 N HCl (3 ml) at 20°, and added to N aq NH_3 (0·2 ml). The products were analyzed as above, and the results plotted in the same way. The half-times of hydrolysis of the uridine 2'- and the thymidine 5'-ketals were found to be 24 and 10·5 min, respectively.

(*c*) *A mixture of* 2'-O-*methoxytetrahydropyranyl-uridine and -adenosine.* After suitable intervals of time, samples (0·2 ml) were removed from a soln (pH 2·3) of 2'-O-methoxytetrahydropyranyluridine (0·035 g, 0·098 mmole) and 2'-O-methoxytetrahydropyranyladenosine (0·040 g, 0·105 mmole) in 0·02 N HCl (3·5 ml) at 20°, and added to N aq NH_3 (0·2 ml). The products were analyzed as above, and the uridine and adenosine 2'-ketals were both found to have $t_{\frac{1}{2}}$ = 100 min at pH 2·3.

Acknowledgement—Two of us (R.S. and J.E.S.) thank the S.R.C. for the award of Research Studentships.

REFERENCES

[1] W. E. Parham and E. L. Anderson, *J. Am. Chem. Soc.* **70**, 4187 (1948).
[2] H. J. E. Loewenthal, *Tetrahedron* **6**, 303 (1959).
[3] C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.* 1190 (1951).
[4] A. N. de Belder, P. J. Garegg, B. Lindberg, G. Petropavlovskii and O. Theander, *Acta Chem. Scand.* **16**, 623 (1962).
[5] B. E. Griffin, M. Jarman and C. B. Reese, *Tetrahedron* **24**, 639 (1968).
[6] See B. E. Griffin and C. B. Reese, *Ibid.* **25**, 4057 (1969) and other papers in this series.
[7] R. Saffhill, Ph.D Thesis, Cambridge University, p 97 (1968).
[8] M. M. Kreevoy and R. W. Taft, Jr., *J. Am. Chem. Soc.* **77**, 3146, 5590 (1955).
[9] H. P. M. Fromageot, B. E. Griffin, C. B. Reese and J. E. Sulston, *Tetrahedron* **23**, 2315 (1967).
[10] A. Hampton, J. C. Frantantoni, P. M. Carrole and S. Wang, *J. Am. Chem. Soc.* **87**, 5481 (1965).
[11] C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, p 334, Bell, London (1953).
[12] H. C. Brown, R. S. Fletcher and R. B. Johannensen, *J. Am. Chem. Soc.* **73**, 212 (1951).
[13] D. G. Lindsay and C. B. Reese, *Tetrahedron* **21**, 1673 (1965).
[14] S. Olsen and R. Bredock, *Chem. Ber.* **91**, 1589 (1958).
[15] J. P. Horwitz, J. A. Urbanski and J. Chua, *J. Org. Chem.* **27**, 3300 (1962).
[16] D. P. L. Green, T. Ravindranathan, C. B. Reese and R. Saffhill, *Tetrahedron* **26**, 1031 (1970).
[17] L. Claisen, *Chem. Ber.* **31**, 1019 (1898).