NUCLEIC ACID COMPONENTS AND THEIR ANALOGUES. CLIII.*

PREPARATION OF 2'-DEOXY-L-RIBONUCLEOSIDES OF THE PYRIMIDINE SERIES**

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Received January 26th, 1972

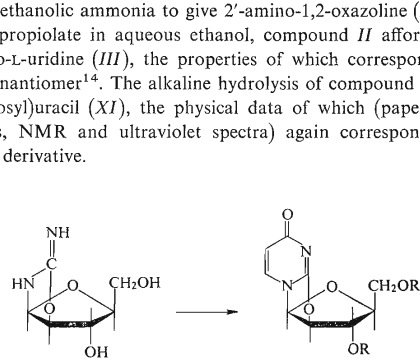
The reaction of L-arabinose (*I*) and cyanamide gave 2'-amino-1,2-oxazoline (*II*) which was treated with methyl propiolate to afford $O^{2,2'}$-anhydro-L-uridine (*III*). The reaction of *III* 3',5'-di-O-benzoyl derivative (*IV*) and hydrogen chloride led to the 2'-deoxy-2'-chloro derivative *Va*; the treatment of *IV* with lithium iodide in dimethylformamide in the presence of hydrogen chloride gave a mixture of stereoisomeric 2'-deoxy-2'-iodo derivatives *Vb,c*. By the action of tri-n-butyltin hydride and the subsequent debenzoylation, compounds *V* afford 2'-deoxy-L-uridine (*VII*). The reaction of 3',5'-di-O-benzoyl-2'-deoxy-L-uridine (*VI*) and phosphorus pentasulfide led to the 4-thiouracil derivative *XIII* which was converted into 2'-deoxy-L-cytidine (*XIV*) by heating with methanolic ammonia. Treatment of the nucleoside *VII* with formaldehyde in alkali and the subsequent acid catalysed etherification with ethanol gave 5-ethoxymethyl-2'-deoxy-L-uridine (*XXI*), the catalytic hydrogenation of which led to 2'-deoxy-L-thymidine (*XXII*). 2'-Deoxy-5-bromo-L-uridine (*XXIV*) was prepared by bromination of the nucleoside *VII*. 5-Methyluridine (*XV*) was converted into the $O^{2,2'}$-anhydro derivative *XVI* and the benzoyl derivative *XVII*. Treatment of compound *XVII* with lithium iodide led to the iodo derivative *XVIII*, the tri-n-butyltin hydride reduction of which afforded 3',5'-di-O-benzoyl-2'-deoxythymidine *XIX*. Authentic *XIX* was prepared by benzoylation of 2'-deoxythymidine with benzoyl cyanide.

In some earlier papers of this Series, the preparation of L-ribonucleosides[2] and the corresponding nucleotide and oligonucleotide derivatives[2,3] has been reported along with some biochemical observations on these compounds[2-5]. Attention has been paid also to enantiomers of deoxyribonucleic acid components, namely, 2'-deoxy-L-ribonucleosides (*cf.* the preparation of 2'-deoxy-L-thymidine[6] and 2'-deoxy-L-adenosine[7] by the nucleoside condensation of the corresponding base and protected 2'-deoxy-L-ribose). The latter procedure, however, does not appear suitable for preparation of 2'-deoxy-L-ribonucleosides on a larger scale. Another route consists in the use of L-ribonucleosides as the starting material. Thus in the D-series, the 2'-deoxy-2'-halo derivatives[8-10] or the 2'-deoxy-2'-mercapto derivatives[11,12] have been successfully applied as intermediates. In the present paper, we wish to report the use of the former 2'-deoxy-2'-halo derivatives in the L-series.

* Part CLII: This Journal *37*, 2798 (1972).

** Some partial results have been reported in a preliminary communication[1].

The recently published[13] preparation of $O^{2,2'}$-anhydrouridine from D-arabinose is of great importance for the whole process. The reaction conditions were somewhat modified to obtain higher yields. Thus, L-arabinose reacts with cyanamide in aqueous methanolic ammonia to give 2'-amino-1,2-oxazoline (*II*). When refluxed with methyl propiolate in aqueous ethanol, compound *II* affords a high yield of $O^{2,2'}$-anhydro-L-uridine (*III*), the properties of which correspond to those of the appropriate enantiomer[14]. The alkaline hydrolysis of compound *III* leads to 1-(β-L-arabinofuranosyl)uracil (*XI*), the physical data of which (paper chromatography, eletrophoresis, NMR and ultraviolet spectra) again correspond to those of the enantiomeric derivative.



II

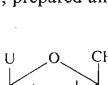
III, R = H
IV, R = C_6H_5CO

VI, R = C_6H_5CO
VII, R = H

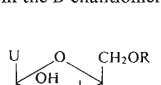
Va, R^1 = H, R^2 = Cl
Vb, R^1 = H, R^2 = I
Vc, R^1 = I, R^2 = H

The reaction of compound *III* with lithium iodide or sodium iodide in dimethylformamide and in the presence or absence of an acid catalyst does not lead to satisfactory results being accompanied by a considerable destruction of the nucleoside derivative. On the other hand, the opening of the $O^{2,2'}$-anhydro linkage by the halide ion should be much more easier in the case of the corresponding 3',5'-dibenzoate *IV* because of the participation of the vicinal 3'-benzoyl group. The reported[15] ben-

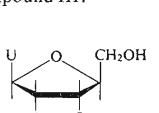
zoylation procedure of the D-enantiomer of compound *III* leads to a product which is highly contaminated by coloured by-products. On the other hand, the reaction of compound *III* with a small excess of benzoyl cyanide[16,17] in dimethylformamide and in the presence of triethylamine affords an almost quantitative yield of the benzoate *IV* which crystallises directly from the reaction mixture. Compound *IV* of the L-series is identical (except for the $[\alpha]_D^{20}$ value) with the corresponding D-enantiomer, prepared analogously from the D-enantiomer of compound *III*.



VIII, R = C_6H_5CO
X, R = H



IX, R = C_6H_5CO
XI, R = H



XII

U = uracil residue

The reaction of compound *IV* with anhydrous hydrogen chloride in dimethylformamide affords quantitatively the 2′-deoxy-2′-chloro derivative *Va*. The reaction proceeds stereospecifically under the formation of a derivative of the *ribo* configuration as shown by NMR spectrum (the presence of a single doublet for $H_{1'}$) and by reaction of compound *Va* with triethylamine in an aprotic solvent leading quantitatively to the starting derivative *IV*.

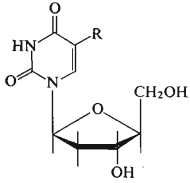
No 2′-deoxy-2′-iodo derivative is formed by reaction of compound *IV* with anhydrous hydrogen iodide in dimethylformamide or with lithium iodide in the presence of boron trifluoride etherate. On the other hand, the use of excess anhydrous lithium iodide in dimethylformamide and in the presence of more than one equivalent of hydrogen chloride leads to an approximately 70% yield of the 2′-deoxy-2′-iodo derivative in the form of a stereoisomeric mixture containing the derivatives *Vb* and *Vc* roughly in the equimolar ratio; longer reaction periods result in a higher proportion of the *arabo* isomer (*Vc*) up to 70%. The mixture of isomers was analysed by means of NMR spectroscopy. The signals of $H_{1'}$ doublets of both isomers were assigned on the basis of the reaction of the mixture *Vb,c* with triethylamine in acetonitrile (removal of the isomer *Vb*). The mixture does not contain any 2′-deoxy-2′-chloro derivative *Va*. Furthermore, compounds *Vb,c* are not formed *via* the derivative *Va* as shown by a separate reaction of authentic *Va* with lithium iodide and hydrogen chloride; such a reaction does not afford any 2′-deoxy-2′-iodo derivatives when performed under conditions identical with those employed in the reaction of compound *IV* (the reaction of compound *Va* with sodium iodide in acetone results in a quantitative recovery of compound *IV*). It may be consequently assumed that the attack of the iodide ion on the protonated form of compound *IV* leads to the formation of the derivative *Vb* of the *ribo* configuration; the subsequent attack of the iodide ion on compound *Vb* results in a S_N2 reaction leading to the *arabo*-isomer *Vc*.

In the reaction of compound *IV* with lithium iodide, the 3′,5′-dibenzoyl derivatives *VIII* and *IX* are formed as by-products. The mixture of *VIII* and *IX* is separated from the mixture of *Vb,c* by crystallisation and column chromatography on silica gel. The *arabo*-isomer *IX* is finally ob-

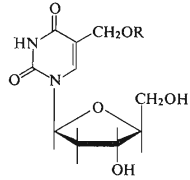
tained in the pure state by crystallisation. The formation of compound *IX* may be ascribed to the hydrolysis of the protonated form of compound *IV*. The *ribo*-isomer *VIII* is obviously formed by hydrolysis of the intermediary 2',3'-cyclic orthobenzoate. The nucleosides *X* and *XI* are obtained by deblocking of the dibenzoates *VIII* and *IX* and the subsequent separation on the borate form of DEAE-cellulose or conversion of the nucleoside *X* to the 2',3'-O-isopropylidene derivative *XII*. The nucleoside *X* is identical with the earlier reported specimen[2]. Compound *IX* is in every respect identical with the hydrolytical product of compound *III*. As shown by elemental analysis and chromatographic behaviour, the isopropylidene derivative *XII* of the L-series is identical with the D-enantiomer[18] and is converted into L-uridine (*X*) by refluxing in 80% CH_3COOH.

The halo derivative *Va* is converted on heating with Raney nickel to the 2'-deoxy derivative *VI*, but the yield is low. On the other hand, the reflux of halo derivatives *V* (the chloro derivative *Va* requires longer reaction periods) in the benzenic solution of tri-n-butyltin hydride[17] in the presence of a catalyst leads to almost quantitative yields of 3',5'-di-O-benzoyl-2'-deoxy-L-uridine (*VI*) identical with the D-enantiomer obtained by reaction of 2'-deoxyuridine with benzoyl cyanide[16]. Deblocking of compound *VI* with methanolic sodium methoxide afforded 2'-deoxy-L-uridine (*VII*), the structure of which was confirmed on comparison with the D-enantiomer (NMR and CD spectra). On treatment with phosphorus pentasulfide in dioxane[19], the 3',5'-dibenzoyl derivative *VI* was converted into the 4-thio derivative *XIII*, the ammonolysis of which afforded 2'-deoxy-L-cytidine (*XIV*), identical with the D-enantiomer.

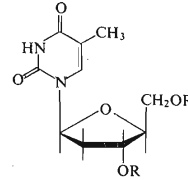
The naturally occurring deoxyribonucleic acids do not mostly contain 2'-deoxyuridine but 2'-deoxythymidine. In connection with biochemical investigations on L-enantiomers, it was therefore necessary to attempt also the synthesis of 2'-deoxy-L-thymidine (*XXII*). In this case, it is not possible to proceed analogously to the preparation of compound *III* from the L-arabinose derivative *II* but it would be necessary to start from 1-(β-L-ribofuranosyl)thymine[2]. The whole reaction sequence was first performed in the D-series. Thus, 5-methyluridine (*XV*) was converted[14] to the $O^{2,2'}$-anhydro derivative *XVI*, the benzoylation of which with benzoyl cyanide afforded the 3',5'-dibenzoate *XVII*. The preparation of compound *XVIII* on treatment of the dibenzoate *XVII* with lithium iodide was effected analogously to the preparation of compound *V*, but in a lower yield. The iodo derivative *XVIII* was



VII, R = H
XXIV, R = Br



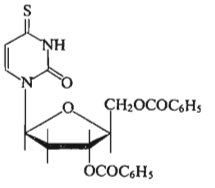
XX, R = H
XXI, R = C_2H_5



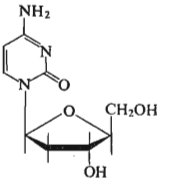
XXII, R = H
XXIII, R = COC_6H_5

reduced with tri-n-butyltin hydride to 3′,5′-di-O-benzoyl-2′-deoxythymidine (*XIX*) which was identical with an authentic specimen obtained from 2′-deoxythymidine by the action of benzoyl cyanide[16]. This route, however, does not seem suitable for the preparation of the L-enantiomer of compound *XIX* because of the unsatisfactory yields of compound *XVIII* and the anhydro derivative *XVI* or its L-enantiomer.

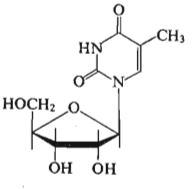
The other route for the preparation of 2′-deoxy-L-thymidine (*XXII*) consists in introduction of a methyl group into position 5 of the uracil ring of compound *VII*. This introduction might be accomplished either by reaction of the corresponding organolithium derivative with methyl iodide[20] or by hydroxyalkylation of position 5 with formaldehyde and hydrogenolysis of the resulting 5-hydroxymethyl derivative[21–23]. The hydroxyalkylation method appeared more suitable since it is not accompanied by side reactions. Thus, the reaction of 2′-deoxy-L-uridine (*VII*) with formaldehyde in 0·5M-NaOH gave the 5-hydroxymethyl derivative *XX*, the treatment of which with ethanol led to the 5-ethoxymethyl derivative *XXI*. The product *XXI* can be readily separated from the unreacted starting *VII*. The yield of the conversion *VII* → *XXI* is 50–60%. The hydrogenation of compound *XXI* over palladium on charcoal afforded 2′-deoxy-L-thymidine (*XXII*) as the sole product. When some contaminants interfere in the crystallisation, the nucleoside *XXII* is converted into the well crystallising 3′,5′-dibenzoyl derivative *XXIII* from which the pure *XXII* is recovered on treatment with methanolic sodium methoxide.



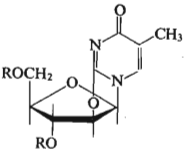
XIII



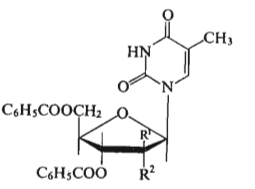
XIV



XV



XVI, R = H
XVII, R = C_6H_5CO



XVIII, R^1, R^2 = H, I
XIX, $R^1 = R^2$ = H

The resulting 2'-deoxy-L-thymidine (*XXII*) was analytically pure and its structure was confirmed by UV and NMR spectra. The chromatographic behaviour of the nucleoside *XXII* of the L-series is identical with that of the authentic D-enantiomer. A similar identity is shown by the dibenzoate *XXIII* and the authentic *XIX* of the D-series.

5-Bromo-2'-deoxyuridine is one of the most attractive 2'-deoxynucleosides because of the high antiviral and bacteriostatic activity[24]. The corresponding L-enantiomer *XXIV* was prepared by bromination of compound *VII* according to the known procedure[25,26]. None of compounds *XXIV*, *XIV*, and *VII* shows any bacteriostatic activity on the growth of *Escherichia coli* in a synthetic medium up to the concentration of 1 000 μg per ml, probably because of the low ability of 2'-deoxy-L-ribonucleosides to penetrate the bacterial cell wall[4]. The present method opened the route for preparing enantiomers of the naturally occurring 2'-deoxyribonucleosides and for their biochemical investigations. This route is also suitable for a simple synthesis of some 2'-deoxy-D-ribonucleosides from D-arabinose on a large scale.

EXPERIMENTAL

Methods. Unless stated otherwise, the solutions were taken down on a rotatory evaporator at 40°C/15 Torr. The substances were dried over phosphorus pentoxide at 0·1 Torr. Paper chromatography was performed by the descending technique on paper Whatman No 1 (preparative runs on paper No 3 MM) in the solvent systems S_1, 2-propanol–concentrated aqueous ammonia–water (7 : 1 : 2), and S_2, 1-butanol saturated with water. Paper electrophoresis was carried out on paper Whatman No 3 MM by the technique of Markham and Smith[27] (40 Volt/cm) in E_1, 0·1 M triethylammonium hydrogen carbonate (pH 7·5) or E_2, 0·2M triethylammonium borate (pH 7·5). For the R_F values see Table I. Thin-layer chromatography was performed on Silufol UV_{254} silica gel plates (manufactured by Kavalier Glassworks, Votice, Czechoslovakia) in the solvent systems S_3, chloroform–ethanol (95 : 5); S_4, chloroform–ethanol (90 : 10); and S_5, ethyl acetate–benzene (30 : 70). Preparative thin-layer chromatography was performed on loose silica gel (30—50 mesh) containing a fluorescent indicator (produced by Service Laboratories of this Institute, Prague-Suchdol), 40 × 16 × 0·4 cm. Column chromatography on DEAE-cellulose was performed with the use of a 80 × 4 cm column packed with Cellex D (standard capacity; produced by Calbiochem, Los Angeles, U.S.A.) in the HCO_3^- form and linear gradient of triethylammonium hydrogen carbonate[2,3] (pH 7·5), or, in the borate form and linear gradient of triethylammonium borate[2] (pH 7·5). The course of elution was checked by the Uvicord apparatus. The volatile buffers were removed by coevaporation with methanol. NMR spectra were taken on a Varian 100 apparatus in hexadeuteriodimethyl sulfoxide (hexamethyldisiloxane as internal standard). The chemical shifts (δ) are expressed as p.p.m., the interaction constants in Hz. CD spectra were recorded in aqueous solutions on a Jouan Dichrograph CD·185 apparatus. For the data see the text (wavelengths of maxima and intersections in nm, Θ values in parentheses). Ultraviolet absorption spectra were taken on a Beckman Model DU apparatus in aqueous or methanolic solutions.

Starting materials and reagents. Cyanamide was prepared by the reported procedure[28] and the crude residue of the ethereal filtrate was directly used. Tri-n-butyltin hydride was prepared[29] from tri-n-butyltin chloride (Aldrich, U.S.A.) and applied without distillation as a 20% solution in benzene (the solution may be stored for several months at 4°C under exclusion of moisture).

2-Amino-β-L-arabinofurano[1′,2′:4,5]oxazoline* (*II*)

A mixture of L-arabinose (170 g; 1·13 mol), crude cyanamide (100 g), methanol (300 ml), and 6M-NH_4OH (50 ml) was stirred at room temperature for 3 days and then kept at −10°C overnight. The product was collected with suction, washed with four 100 ml portions of methanol and two 100 ml portions of ether, and dried *in vacuo*. Yield, 136·5 g (69%) of the analytically pure compound *II*, m.p. 180°C. For $C_6H_{10}N_2O_4$ (174·2) calculated: 41·36% C, 5·78% H, 16·08%N; found: 41·38% C, 5·94% H, 16·23% N. Optical rotation: $[\alpha]_D^{25}$ −20·6° (*c* 1·0; water). The D-enantiomer of compound *II* was prepared analogously in 72% yield; m.p. 181°C; $[\alpha]_D^{25}$ +21·2° (*c* 1·0; water).

$O^{2,2'}$-Anhydro-L-uridine (*III*)

A solution of compound *II* (120 g; 0·69 mol) and methyl propiolate (120 ml) in 50% aqueous ethanol (1 800 ml) was refluxed for 5 h and then concentrated under diminished pressure to the half of the original volume. The product was collected with suction, washed with ethanol and ether, and dried under diminished pressure. The mother liquor was concentrated to the volume of about 250 ml, the concentrate precipitated with acetone (1 000 ml), the solid collected with suction, and washed with acetone and ether to afford another crop of the product. Over-all yield, 101 g (65%) of compound *III*, m.p. 239°C. For $C_9H_{10}N_2O_5$ (226·1) calculated: 47·78% C, 4·45% H, 12·38% N; found: 47·33% C, 4·53% H, 12·15% N. Ultraviolet spectrum (methanol): λ_{max} 226 and 248 nm. λ_{min} 235 nm; ε_{248} 8 300, ε_{260} 6 500; $A_{250/260}$ 1·26, $A_{280/260}$ 0·12. NMR spectrum: $H_{1'}$ (d, 1 H) 6·32, $J_{1',2'} = 5·8$, $H_{2'}$ (d, 1 H) 5·23, $H_{3'}$ (m, 1 H) 4·44, $J_{2',3'} = 0·8$, $H_{4'}$ (m, 1 H) 4·24, $J_{3',4'} = 1·6$, 2 $H_{5'}$ (2 xq, 2 H) 3·30, $J_{4',5''} = 4·7$, $J_{4',5''} = 5·6$, $J_{gem} = 11·8$; (d, 1 H), 5·86, H_6 (d, 1 H) 7·77, $J_{5,6} = 7·4$, OH (d, 1 H) 5·88, OH (d, 1 H) 4·96, $J_{OH,H_{3'}} = 4·5$, $J_{OH,5'} = 5·0$ (these data are identical with those of the authentic D-enantiomer *III*, prepared according to ref.[14]). CD spectrum: 274 (+900), 266·5 (0), 241·5 (−13 980), 225·5 (0), 217 (+8 340), 203·5 (+2 240).

3′,5′-Di-O-benzoyl-$O^{2'2'}$-anhydro-L-uridine (*IV*)

A suspension of compound *III* (100 g; 0·43 mol) and benzoyl cyanide (125 g; 0·95 mol) in dimethylformamide (800 ml) was treated under stirring with 15 ml of triethylamine (exothermic reaction). The mixture dissolved rapidly and deposited spontaneously the product. The mixture was diluted with dimethylformamide (200 ml), stirred for 3 h, and finally diluted with ethanol (100 ml). The whole was poured into 2 litre of ether, the precipitate collected with suction, washed with ether, and dried. Yield, 178 g (95%) of pure *IV*, m.p. 257—258°C. For $C_{23}H_{18}N_2O_7$ (434·4) calculated: 63·59% C, 4·17% H, 6·45% N; found: 63·39% C, 4·42% H, 6·27% N. Optical rotation: $[\alpha]_D^{25}$ +48·3° (*c* 0·5; dimethylformamide). The D-enantiomer of compound *IV* was prepared analogously from 5 g of the D-enantiomer of compound *III*; yield, 97%; m.p. 262°C (reported[15], m.p. 262°C); $[\alpha]_D^{25}$ −46·5° (*c* 0·5; dimethylformamide).

3′,5′-Di-O-benzoyl-2′-chloro-2′-deoxy-L-uridine (*Va*)

A mixture of compound *IV* (43·5 g; 0·1 mol), dimethylformamide (400 ml) and 6M-HCl in dimethylformamide (80 ml) was stirred at 100°C for 90 min under exclusion of atmospheric moisture, cooled down, and poured under stirring into 3 l of water. The precipitate of compound *Va* was collected with suction, washed with 2 l of water, and recrystallised from ethanol (1 200 ml).

* This procedure is in principle identical with that independently worked out by Wechter[30] the product obtained by both methods exhibits identical physical data.

The crystals were collected with suction, washed with ethanol and ether, and dried under diminished pressure. Yield, 41·2 g (87·5%) of compound *Va*, m.p. 166–167°C. For $C_{23}H_{19}ClN_2O_7$ (470·9) calculated: 58·67% C, 4·06% H, 7·53% Cl, 5·95% N; found: 58·62% C, 4·1% H, 7·43% Cl, 5·95% N. Optical rotation: $[\alpha]_D^{25}$ +19·4° (*c* 0·5; dimethylformamide). NMR spectrum: $H_{1'}$ (d) 6·12 ($E_{1',2'} = 4·6$); $H_{4'} + H_{2'} + 2 \times H_{2'}$ (m) 4·45–4·85; H_5 (d) 5·52 ($J_{5,6} = 8·0$); $H_{3'}$ (t) 5·56 ($J_{2',3'} = 5·0$, $J_{3',4'} = 5·0$); H_6 (d) 7·35 ($J_{5,6} = 8·0$); NH (br s) 9·62; arom. (m) 7·2–7·5, 7·80–8·05.

Reaction of Compound *IV* with Lithium Iodide

a) *In the presence of hydrogen chloride.* Freshly fused lithium iodide (200 g; 1·5 mol) was dissolved at 100°C in 1 l of dimethylformamide under stirring and exclusion of atmospheric moisture. The solution was treated first with compound *IV* (100 g; 0·23 mol) and then at 100°C

TABLE I
R_F Values

Compound	S_1	S_2	S_3	S_4	S_5
Uridine	0·50	0·14	—	0·10	—
III	0·63	0·16	—	0·23	—
IV	—	—	0·30	—	—
V	—	—	0·45	—	0·33
VI	—	—	0·37	—	0·18
VII	0·60	0·31	—	0·12	0·12
VIII	—	—	0·38	0·66	0·04
IX	—	—	0·38	0·66	0·04
X	0·50	0·14	—	0·10	—
XI	0·60	0·24	—	0·12	—
XII	0·78	—	0·25	0·46	—
XIII	—	—	—	—	0·60
XIV	0·61	0·35	—	—	—
XV	0·58	—	—	0·27	—
XVI	0·66	—	—	0·08	—
XVII	—	—	—	0·20	—
XVIII	—	—	0·48	—	0·42
XIX	—	—	0·42	—	0·25
XX	0·60	—	—	0·12	—
XXI	0·67	—	—	0·26	—
XXII	0·68	—	—	0·16	—
XXIII	—	—	0·42	—	0·25
XXIV	0·54	—	—	—	—
2'-Deoxyuridine	0·60	0·31	—	0·12	—
2'-Deoxycytidine	0·62	0·35	—	—	—
2'-Deoxythymidine	0·68	—	—	0·16	—

with 50 ml of 6M-HCl in dimethylformamide in one portion (this sequence is important for a good yield of compound *V*). After 15 min of stirring, a solution was obtained which was treated at 100°C with additional 25 ml of 6M-HCl in dimethylformamide in the course of 30 min. The mixture was heated at 100°C for 90 min, cooled down with ice, and poured under stirring into 4 l of ice-cold water. The crystalline yellow precipitate was collected with suction and washed with 1 l of water. The moist product was recrystallised from 1 500 ml of ethanol (the product must be dissolved under stirring as fastly as possible; the boiling solution deposits suddenly the sparingly soluble crystalline form of the pure *V*). The crystals were collected with suction, washed with ethanol (500 ml) and ether, and dried. The filtrate was evaporated to dryness, the residue extracted with methylene chloride (500 ml), the extract washed with 10% aqueous sodium thiosulfate (100 ml) and two 100 ml portions of water, dried over magnesium sulfate, and concentrated to a small volume. The concentrate was applied to a column of Pitra silica gel (80—100 mesh; 750 g) packed in methylene chloride. The column was eluted with chloroform containing 2% of ethanol and the course of elution (500 ml fractions) checked by thin-layer chromatography in the solvent system S_3. Fractions 1—5 were pooled, evaporated, and the residue crystallised from 100 ml of ethanol to afford compounds *Vb,c*. Total yield, 87 g (67%); m.p. 178°C. For $C_{23}H_{19}IN_2O_7$ (562·3) calculated: 49·12% C, 3·40% H, 22·56% I, 4·98% N; found: 48·92% C, 3·52% H, 22·90% I, 5·12% N. NMR spectrum: $H_{1'}$ in *Vb* (d) 6·19, $J_{1',2'}$ 5·0; $H_{1'}$ in *Vc* (d) 6·46, $J_{1',2'} = 7·0$ (intensity ratio 7 : 3); mixture of *Vb,c*: arom. (m, 10 H) 7·30—7·70; arom. (m, 5 H) 7·95—8·20; NH (br s) 11·34. The elution of compounds *Vb,c* was followed by elution with 3 litre of methanol. The methanolic eluate was evaporated and the residue dried under diminished pressure to afford 27 g (60 mmol; 26%, referred to the starting *IV*) of a mixture of the dibenzoate *VIII* and *IX*. This mixture (500 mg) was treated with 10 ml of 0·1M methanolic sodium methoxide and the whole mixture heated at 50°C for 3 h (the debenzoylation was quantitative after this period of time, as shown by chromatography in the solvent system S_1 and S_4) and then processed by chromatography (S_1) and electrophoresis (E_2) to afford the *arabino* derivative *XI* (from *IX*) and the *ribo* isomer *X* (from *VIII*) in the ratio 7 : 3. The original mixture (26·5 g) of dibenzoates *VIII* and *IX* was dissolved in ethanol (200 ml) and the solution kept in a refrigerator to deposit 13 g (35 mmol) of compound *IX*, m.p. 184—185°C. For $C_{23}H_{20}N_2O_8$ (452·4) calculated: 61·06% C, 4·45% H, 6·19% N; found: 60·95% C, 4·39% H, 6·07% N. Optical rotation: $[\alpha]_D^{25}$ −6·8° (*c* 0·5; dimethylformamide). NMR spectrum: $H_{1'}$ (d, 1 H) 6·26; $H_{2'}$ (m, 1 H) 4·40—4·60, $J_{1',2'} = 3·5$; $H_{3'}$ (m, 1 H) 5·39, $J_{2',3'} = 2·0$; $H_{4'}$ (m, 1 H) 4·40—4·60, $J_{3',4'} = 1·0$; 2 $H_{5'}$ (m, 2 H) 4·60—4·85; H_5 (d, 1 H) 5·57; H_6 (d 1 H) 7·68, $J_{5,6} = 8·0$, $J_{5,NH} = 1·5$; NH (br s, 1 H) 10·99; OH (d, 1 H) 6·0; $J_{OH,H_2} = 4·5$; arom (m, 6 H) 7·30—7·65; arom (m, 4 H) 7·95—8·15. Compound *IX* is converted on treatment with methanolic sodium methoxide into compound *XI* as the sole product. b) *In the presence of trifluoroacetic acid.* A mixture of *IV* (0·5 mmol), fused lithium iodide (1 mmol), and dimethylformamide (3 ml) was equilibrated at 100°C and treated with trifluoroacetic acid (0·2 ml). The reaction course was checked by thin-layer chromatography in the solvent system S_3. After 30 min, the reaction mixture contained compounds *VIII* and *IX* only, as indicated by R_F values. c) *In the presence of boron trifluoride etherate.* The mixture was prepared as in paragraph *a*) and treated with boron trifluoride etherate (0·2 ml). After 30 min at 100°C, the reaction mixture contained (in addition to degradation products and traces of compound *V*) as the main product the dibenzoates *VIII* and *IX*, as shown by the corresponding R_F values. d) *Reaction with sodium iodide in the presence of hydrogen chloride.* A mixture of compound *IV* (2 g; 4·6 mmol), anhydrous sodium iodide (4 g), dimethylformamide (10 ml), and 6M-HCl in dimethylformamide (1 ml) was kept at 100°C for 1 h, diluted with chloroform (100 ml), washed with two 20 ml portions of 10% aqueous sodium thiosulfate, dried over magnesium sulfate, evaporated, and the residue chromatographed in the solvent system S_3. The bands of compounds *V*, *VIII* and *IX* were eluted with methanol (200 ml), the eluates evaporated, and the residues

dried under diminished pressure to afford 15% of compound *V* and 53% of the mixture of compounds *VIII* and *IX*. All these compounds were identical with the corresponding above mentioned specimens (solvent systems S_3 to S_5).

Reactions of Compound *Va*

a) *With lithium iodide and hydrogen chloride.* A mixture of anhydrous lithium iodide (2 g), dimethylformamide (10 ml), and 6M-HCl in dimethylformamide (1 ml) was treated at 100°C with compound *Va* (1·0 g) and then heated at 100°C for 2 h under exclusion of atmospheric moisture. The resulting solution was poured into water (200 ml). The precipitate was collected with suction, washed with water (500 ml), and recrystallised from ethanol to afford 0·85 g of the starting compound *Va*, m.p. 166–167°C. The mother liquor did not contain any additional compounds, as shown by thin-layer chromatography in the solvent system S_3. A similar result was obtained when the experiment was performed in the absence of hydrogen chloride. b) *With sodium iodide in acetone.* A mixture of compound *Va* (0·86 g; 2 mmol), sodium iodide (1·5 g; 10 mmol), and acetone (25 ml) was refluxed for 8 h, diluted with water (100 ml), the precipitate collected with suction, washed with water, ethanol, and ether, and dried under diminished pressure to afford 0·80 g (92%) of the analytically pure compound *IV*, identical with an authentic specimen on thin-layer chromatography in the solvent system S_3. M.p. 262°C. Optical rotation: $[\alpha]_D^{25}$ +48·7° (*c* 0·5; dimethylformamide).

Reaction of Compounds *Vb,c* with Triethylamine in Acetonitrile

Triethylamine (0·5 ml; 3·6 mmol) was added to a suspension of compounds *Vb,c* (1·1 g; 2 mmol) in acetonitrile (20 ml) and the whole mixture was stirred at room temperature overnight. The precipitate was collected with suction, washed with acetonitrile, and dried under diminished pressure to afford 0·44 g (50%) of compound *IV* which was identified on comparison with an authentic specimen by chromatography in the solvent system S_3. The filtrate was chromatographed on one plate of loose silica gel in S_3 to remove the remaining compound *IV*. The band of *Vb,c* was eluted with methanol (100 ml), the eluate evaporated, and the residue crystallised from ethanol. Yield, 0·35 g (31·8%) of the mixture *Vb,c*, m.p. 178°C, $[\alpha]_D^{25}$ +21·5° (*c* 0·5; dimethylformamide). This mixture contains about 90% of the *arabo*-isomer *Vc*, as indicated by NMR spectrum. To determine the ratio of isomers in the starting material, the original mixture of *Vb,c* was rechromatographed in the solvent system S_3 and recrystallised under the same conditions as above. As shown by NMR measurement, the content of the *arabo*-isomer was about 60%, $[\alpha]_D^{25}$ +30·0° (*c* 0·5; dimethylformamide).

L-Uridine (*X*) and 1-(β-L-Arabinofuranosyl)uracil (*XI*)

a) The mixture (13 g) of the dibenzoates *VIII* and *IX* resulting after removal of compound *IX* by crystallisation, was added to 100 ml of 0·1M methanolic sodium methoxide, the whole kept at 50°C for 3 h, and neutralised by the addition of Dowex 50 (H^+) ion exchange resin. The resin was then filtered off, washed with methanol (200 ml), the combined filtrates evaporated to dryness, the residue dissolved in water (200 ml), the aqueous solution washed with two 50 ml portions of ether, and concentrated to the volume of about 50 ml. The concentrate was adjusted by the addition of aqueous ammonia to the value of pH 8, treated with 15 ml of 2M triethylammonium borate (pH 7·5), diluted with water (100 ml), and passed through a column of DEAE-cellulose in the borate cycle. The column was eluted with water to the drop of ultraviolet absorption (compound *XI*) and then with 0·1M triethylammonium borate (compound *X*). The buffer was removed

by codistillation with methanol and the residue was crystallised from ethanol (50 ml) to afford 3·6 g (15 mmol) of L-uridine (*X*), m.p. 163°C, identical with an authentic specimen on chromatography in S_1 and S_2, and electrophoresis in E_2. The aqueous fraction was evaporated, the residue dissolved in ethanol (10 ml), and the solution precipitated with ether (200 ml) to afford 1·0 g (4 mmol) of the amorphous compound *XI*, identical with an authentic specimen in S_1, S_2 and E_2. *b*) The mixture of dibenzoates (100 mmol) *VIII* and *IX* remaining after the isolation of compound *V* was deblocked analogously to paragraph *a*). The residual compounds *X* and *XI* were dried by coevaporation with ethanol and toluene (50 ml each) and then shaken with a mixture of dimethylformamide (80 ml), ethyl orthoformate (30 ml), acetone[18] (20 ml), and 6M-HCl in dimethylformamide overnight. Triethylamine (10 ml) was added, the salt filtered off, washed with ethyl orthoformate (20 ml), the filtrates combined, and evaporated at 40°C/0·1 Torr. The residue was extracted with hot chloroform (500 ml), the extract cooled down, filtered, the solid washed with chloroform (100 ml), the filtrates combined, and concentrated under diminished pressure to a small volume. The solid insoluble in chloroform is chromatographically and electrophoretically identical with compound *XI* (12·2 g; 50 mmol). Chromatography of the filtrate on a column of Pitra silica gel (500 g; 80—100 mesh) and elution with 5% ethanol in chloroform afforded 8·6 g (30 mmol) of the chromatographically pure 2′,3′-O-isopropylidene-L-uridine (*XII*) (after crystallisation from 4 : 1 ethanol–light petroleum). For $C_{12}H_{16}N_2O_6$ (284·2) calculated: 50·69% C, 5·67% H, 9·87% N; found: 50·70% C, 5·93% H, 9·57% N. Compound *XII* was identical with a specimen obtained (yield, 80%) by a known procedure[18] from L-uridine (*X*). When refluxed in 80% aqueous acetic acid for 30 minutes, compound *XII* afforded L-uridine (*X*) as the sole product. CD spectrum: 268 (−5000), 250 (0), 236 (+2640), 226 (+2000), 212 (+4000), 200 (0).

3′,5′-Di-O-benzoyl-2′-deoxy-L-uridine (*VI*)

a) A mixture of compound *Va* (1·0 g), Raney nickel W 4 (2 g), ethanol (100 ml), and calcium carbonate (1 g) was refluxed for 2 h, filtered through a layer of Hyflo Super Cel, the solid washed with ethanol (200 ml), the filtrate and washing evaporated to dryness, and the residue crystallised from ethanol. The crystals were collected with suction, washed with ethanol and ether, and dried to afford 0·20 g (22%) of compound *VI*, identical with the specimen from paragraph *b*). *b*) A mixture of compound *Va* (47 g; 0·1 mol), tri-n-butyltin hydride (120 g), benzene (1000 ml), and azabisisobutyronitrile (0·4 g) was refluxed under stirring for 60 min, cooled down, the solid collected with suction, and washed with benzene (100 ml). The filtrate and washing were combined and concentrated under diminished pressure to the volume of about 200 ml. The concentrate was diluted with light petroleum (800 ml) to deposit an additional crop of compound *VI* which was washed with light petroleum (200 ml) and air-dried. The combined crops of the chromatographically pure (solvent systems S_3 and S_5) compound *VI* were portionwise recrystallised from ethanol (8 l). Yield, 36·5 g (84%); m.p. 218—219°C; $[\alpha]_D^{25}$ +11·2° (*c* 0·5; dimethylformamide). On chromatography in the solvent systems S_3–S_5, compound *VI* was identical with the D-enantiomer[16]. For $C_{23}H_{20}N_2O_7$ (436·4) calculated: 63·29% C, 4·62% H, 6·42% N; found: 63·52% C, 4·78% H, 6·45% N. NMR spectrum: H_1' (q) 6·38 ($J_{1',2'} = 6{\cdot}0$, $J_{1',2''} = 8{\cdot}0$); $H_{2'}$ (oct) 2·65 ($J_{2',1'} = 8{\cdot}0$, $J_{2',3'} = 2{\cdot}0$); $H_{2''}$ (sext) 2·45 ($J_{2'',1'} = 6{\cdot}0$, $J_{2'',3'} = 6{\cdot}0$, $J_{gem} = 14{\cdot}0$); $H_{3'}$ (m) 5·65; $H_{4'}$ (m) 4·55; 2 $H_{5'}$ (m) 4·65—4·80 ($J_{5',4'} = 4{\cdot}0$); NH (br s) 10·92 ($J_{NH,H_5'} = 4{\cdot}0$); H_5 (d) 5·54 ($J_{5,6} = 8{\cdot}0$); H_6, arom (m) 7·30 to 7·70; arom (m) 7·95—8·10. *c*) A mixture of compounds *Vb,c* (50 g; 89 mmol), tri-n-butyltin hydride (72 g), azabisisobutyronitrile (0·4 g), and benzene (600 ml) was refluxed under stirring for one hour and processed analogously to paragraph *b*). Recrystallisation from ethanol afforded 35 g (90%) of compound *VI*, m.p. 218°C, undepressed on admixture with the specimen obtained according to the paragraph *b*).

2′-Deoxy-L-uridine (*VII*)

A mixture of the dibenzoate *VI* (10·0 g; 23 mmol), methanol (100 ml) and 1M methanolic sodium methoxide (25 ml) was stirred at room temperature overnight, diluted with water (500 ml), the aqueous solution washed with three 100 ml portions of ether, and neutralised by the addition of Dowex 50 (H^+) ion exchange resin. The resin was filtered off, the filtrate evaporated under diminished pressure, and the residue crystallised from ethanol to afford 4·1 g (78%) of the analytically pure compound *VII*, m.p. 158°C. For $C_9H_{12}N_2O_5$ (228·2) calculated: 47·36% C, 5·30%H, 12·27% N; found: 47·50% C, 5·36% H, 12·42% N. CD spectrum: 268 (−6720), 250·5 (0), 237 (+4 030), 226 (+3 190), 215 (+4 450). Concentration of the mother liquor afforded additional 0·8 g of compound *VII*; over-all yield 93%.

3′,5′-Di-O-benzoyl-2′-deoxy-4-thio-L-uridine (*XIII*)

The boiling solution of compound *VI* (2·2 g; 5 mmol) in dioxane (120 ml) was treated with phosphorus pentasulfide (1·2 g; 5·6 mmol) and the mixture refluxed under exclusion of atmospheric moisture for 30 minutes. The mixture was then treated with additional phosphorus pentasulfide (1·2 g), refluxed for 20 minutes more, filtered while hot, and the solid washed with dioxane (20 ml). The filtrate and washings were combined, evaporated to dryness under diminished pressure, the residue dissolved in chloroform, and the solution chromatographed on two plates of loose silica gel in the solvent system S_5. Bands of the compound *XIII* (R_F 0·60—0·70) were eluted with methanol (500 ml), the eluate evaporated under diminished pressure, the residue coevaporated with ethanol (50 ml), and then crystallised from ethanol (light petroleum was added to the solution until turbid). Yield, 2·0 g (89%) of compound *XIII*, m.p. 136—137°C. For $C_{23}H_{20}N_2O_6S$ (452·4) calculated: 61·03% C, 4·45% H, 6·19% N, 7·08% S; found: 60·75% C, 4·18% H, 5·75% N, 7·34% S. NMR spectrum: $H_{1'}$ (q, 1 H) 6·31; $H_{2'}$ (q, 1 H) 2·43, $J_{1',2'} = 6{\cdot}0$; $H_{2'}$ (*ribo*) (m, 1 H) 2·75, $J_{1',2''} = 8{\cdot}0$, $J_{gem} = 13{\cdot}0$; $H_{3'}$ (m, 1 H) 5·65, $J_{2',3'} = 6{\cdot}0$, $J_{2'',3'} = 2{\cdot}0$ $H_{4'}$ (m, 1 H) 4·58, $J_{3',4'} = 3{\cdot}0$; $H_{5'}$ (m, 2 H) 4·65—4·75, $J_{4',5'} = 4{\cdot}0$; H_5 (d, 1 H) 6·25; H_6 (d, 1 H) 7·36, $J_{5,6} = 7{\cdot}5$; arom (m, 6 H) 7·40—7·70; (m, 4 H) 7·95—8·10; NH (br s, 1 H) 12·20.

2′-Deoxy-L-cytidine (*XIV*)

A glass ampoule containing 2·0 g (4·4 mmol) of compound *XIII* in 100 ml of 30% methanolic ammonia was heated at 100°C in an autoclave for 10 h. The mixture was evaporated under diminished pressure, the residue diluted with water (150 ml), the aqueous solution washed with three 50 ml portions of ether, the aqueous phase acidified with hydrochloric acid to pH 3·5, and passed through a 100 ml column of Dowex 50 X 8 (NH_4^+) ion exchange resin. The column was eluted with water to the drop of ultraviolet absorption and then with dilute (1 : 5) aqueous ammonia to the disappearance of ultraviolet absorption. The ammonia-containing eluate was evaporated under diminished pressure and the residue coevaporated with ethanol (20 ml). The final residue was dissolved in 5 ml of hot ethanol, the solution diluted with acetonitrile (50 ml) and allowed to crystallise in a refrigerator. The crystals were collected with suction, washed with acetonitrile and ether, and dried to afford 0·61 g of the chromatographically pure (solvent systems S_1 and S_2) compound *XIV*, m.p. 214°C. The properties of compound *XIV* were similar to those of the corresponding D-enantiomer. For $C_9H_{13}N_3O_4$ (227·2) calculated: 47·57% C, 5·76% H, 18·49% N; found: 47·98% C, 5·83% H, 18·48% N. Ultraviolet spectrum (pH 2): λ_{max} 279 nm (ε_{max} 13 200), λ_{min} 240 nm, ε_{260} 6 800; $A_{250/260}$ 0·39, $A_{280/260}$ 2·16, $A_{290/260}$ 1·5. CD spectrum: 272 (−8050), 242 s (−1500), 235·5 (0), 215·5 (+9360).

3′,5′-Di-O-benzoyl-2′-deoxy-L-thymidine (*XXIII*)

A mixture of 2′-deoxy-L-uridine (*VII*; 4·6 g; 20 mmol), 1M-KOH (20 ml), and 37% aqueous formaldehyde (20 ml) was heated at 60°C for 5 days (every 24 h, the mixture was treated with additional 5 ml of 1M-KOH and 5 ml of 37% aqueous formaldehyde)[23]. The mixture was then diluted with an equal volume of water, adjusted to pH 3—4 by the addition of Dowex 50 (H^+) ion exchange resin, filtered, the resin washed with water (200 ml), the filtrate and washings combined, evaporated under diminished pressure, and the residue coevaporated with three 50 ml portions of ethanol. The final residue was dissolved in ethanol (50 ml), the solution made alkaline by the addition of triethylamine, evaporated, the residue coevaporated with toluene (50 ml), and dried over phosphorus pentoxide at 0·1 Torr overnight. A mixture of the residue, ethanol (200 ml), and conc. HCl (0·5 ml) was refluxed for 5 h. After this period of time, the thin-layer chromatography on silica gel in the solvent system S_4 indicated the presence of compound *XXI* contaminated by about 30% of compound *VII*. The reaction mixture was made alkaline with triethylamine, evaporated, and the residue chromatographed on two plates of silica gel in the solvent system S_4. Bands of the product *XXI* were eluted with methanol (200 ml), the eluate evaporated, and the residue dried *in vacuo* to afford 4·4 g (77%) of amorphous *XXI*. This substance was hydrogenated in a mixture of ethanol (200 ml) and concentrated hydrochloric acid (0·5 ml) over 1 g of a 10% palladium on charcoal catalyst (Koch-Light) under atmospheric pressure. When the hydrogenation was finished (after 3 h), the mixture was filtered through Cellit, washed with ethanol (100 ml), the filtrate and washings made alkaline with triethylamine and evaporated to dryness under diminished pressure. The residue was chromatographically homogeneous and identical with compound *XXII* but did not crystallise from ethanol. A mixture of the residual dry *XXII*, acetonitrile (100 ml), benzoyl cyanide (10 g; 75 mmol), and triethylamine (3 ml) was stirred at room temperature for 1 h and then treated with ethanol (5 ml) and ether (300 ml). The crystals of *XXIII* were collected with suction, washed with ether, and recrystallised from ethanol to afford 5·5 g (61%, referred to compound *VII*) of the dibenzoate *XXIII*, m.p. 197°C. For $C_{24}H_{22}N_2O_7$ (450·4) calculated: 64·00% C, 4·92% H, 6·22% N; found: 63·85% C, 5·06% H, 6·38% N. The corresponding properties of compound *XXIII* were identical with those of the D-enantiomer obtained according to ref.[16].

2′-Deoxy-L-thymidine (*XXII*)

A mixture of compound *XXIII* (4·5 g; 10 mmol), methanol (100 ml), and 1M methanolic sodium methoxide was refluxed until a solution was obtained. The solution was kept at room temperature for one hour and then processed analogously to the deblocking of *VI* to *VII*. Crystallisation from ethanol (80 ml) afforded 2·2 g (89%) of the chromatographically (solvent systems S_1, S_2, and S_4) pure compound *XXII*, m.p. 189°C, the properties of which corresponded to those of the D-enantiometer. For $C_{10}H_{14}N_2O_5$ (248·2) calculated: 49·58% C, 5·82% H, 11·56% N; found: 49·61% C, 5·91% H, 11·52% N. Ultraviolet spectrum (pH 2): λ_{max} 267 nm (ε_{max} 9800), λ_{min} 235 nm, ε_{260} 8900, $A_{250/260}$ 0·65, $A_{280/260}$ 0·71. CD spectrum: 275 (−4560), 257 (0) 240·5 (+4780), 230 (+4120), 216 (+6950), 260 (0).

5-Bromo-2′-deoxy-L-uridine (*XXIV*)

A solution of 2′-deoxy-L-uridine (*VII*; 4·0 g; 17·5 mmol) in acetic anhydride (25 ml) was treated under stirring and ice-cooling with bromine (3·14 g *i.e.* 1·0 ml; 0·039 g-at) in acetic acid (2·5 ml). The mixture was kept in a refrigerator overnight, evaporated at 40°C/0·1 Torr, the residue codistilled with six 25 ml portions of toluene and then coevaporated under diminished pressure

with two 20 ml portions of ethanol. The final residue was triturated with ethanol (20 ml) and the mixture treated with ether (50 ml) and light petroleum (200 ml). The solid was collected with suction, washed with light petroleum, air-dried, and then kept in 10% methanolic ammonia (75 ml) at room temperature for 2 days. The mixture was evaporated, the residue coevaporated with three 50 ml portions of ethanol, dissolved in water (25 ml) and the solution applied to a column (100 ml) of Dowex 50 (H^+) ion exchange resin. The solumn was eluted with water and the ultraviolet-absorbing fraction of the eluate evaporated under diminished pressure. The residue was coevaporated with ethanol to deposit crystals which were recrystallised from ethanol, collected with suction, washed with ethanol and ether, and dried under diminished pressure. Yield, 4·2 g (78%) of the bromo derivative[25] *XXIV*. For $C_9H_{11}BrN_2O_5$ (307·2) calculated: 35·18% C, 3·61% H, 26·02% Br, 9·12% N; found: 35·53% C, 3·58% H, 26·24% Br, 9·20% N. Ultraviolet spectrum (pH 2): λ_{max} 277 nm (ε_{max} 9400), λ_{min} 242 nm, ε_{260} 4850, $A_{250/260}$ 0·49, $A_{280/260}$ 1·92, $A_{290/260}$ 1·48. CD spectrum: 283 (−3580), 261 (0), 244·5 (+2530), 235·5 (+2240), 219 (+4620), 211 (0).

1-(β-L-Arabinofuranosyl)uracil (*XI*)

A. A solution of compound *III* (2·26 g; 10 mmol) in 0·05M-NaOH (50 ml) was heated at 50°C for 5 h. After this period of time, the reaction was quantitative as shown by chromatography in the solvent systems S_1 and S_4. The mixture was kept at room temperature overnight and then neutralised with Dowex 50 (H^+) ion exchange resin. The resin was filtered off, washed with water, the filtrate and washings evaporated under diminished pressure, the residue coevaporated twice with ethanol, and recrystallised from ethanol to afford 1·8 g (74%) of compound *XI*.

B. A mixture of compound *IX* (1·1 g; 2·4 mmol), methanol (50 ml), and 1M methanolic sodium methoxide (10 ml) was heated at 50°C for 5 hours and kept at room temperature overnight. As shown by chromatography in the solvent system S_1, the reaction was quantitative. The mixture was evaporated under diminished pressure, the residue dissolved in water (100 ml), the residue neutralised with Dowex 50 (H^+) ion exchange resin, filtered, and the resin washed with water. The filtrate and washings were combined, washed with two 25 ml portions of ether, and evaporated under diminished pressure. The residue was coevaporated with ethanol and then crystallised from ethanol to afford 0·45 g (76%) of compound *XI*, m.p. 223°C, undepressed on admixture with specimen obtained by the procedure *A*. For $C_9H_{12}N_2O_6$ (244·2) calculated: 44·26% C, 4·95% H, 11·74% N; found: 44·50% C, 4·78% H, 11·62% N. CD spectrum: 275 (−15150), 242·5 (0), 235 s (+2550), 215·5 (+9920), 204 (0).

$O^{2,2'}$-Anhydro-5-methyluridine (*XVI*)

A mixture of 5-methyluridine[31] (*XV*; 2·6 g; 10 mmol), diphenyl carbonate (3·0 g), $NaHCO_3$ (100 mg), and dimethylformamide (5 ml) was heated at 150°C for 30 min under occasional stirring and exclusion of atmospheric moisture. The mixture was poured while hot into 250 ml of ether under stirring. The precipitate was collected with suction, washed with ether and chromatographed in methanol on two plates of silica gel. The elution was performed with a mixture of ethanol and chloroform (30 : 70). Bands of the product (R_F value 0·08; the starting compound *XV*, R_F 0·27) were eluted with methanol (800 ml) in a column. The eluate was evaporated and the residue heated in acetonitrile (20 ml) to deposit crystals. Recrystallisation from acetonitrile afforded 1·3 g (56%) of compound *XVI*, m.p. >250°C. For $C_{10}H_{12}N_2O_5$ (240·2) calculated: 50·00% C, 5·03% H, 11·66% N; found: 49·97% C, 5·18% H, 11·88% N. CD spectrum: 241·5 (+13100), 225 (0), 217 (−5160), 205 (−3330).

3′,5′-Di-O-benzoyl-O$^{2,2'}$-anhydro-5-methyluridine (*XVII*)

A solution of compound *XVI* (1·2 g; 5 mmol) and benzoyl cyanide (1·6 g; 12·2 mmol) in dimethylformamide (5 ml) was treated dropwise under stirring with triethylamine (0·5 ml). The mixture was stirred at room temperature for 2 hours and then diluted with acetonitrile (5 ml) and ethanol (1 ml). After 5 min, ether (100 ml) was added under continuous stirring. The precipitate was collected with suction, washed with ether, and recrystallised from ethanol to afford 2·1 g (94%) of compound *XVII* which did not melt up to 250°C. For $C_{24}H_{20}N_2O_7$ (448·4) calculated: 64·28% C, 4·49% H, 6·25% N; found: 60·89% C, 5·68% H, 7·93% N.

3′,5′-Di-O-benzoyl-2′-deoxythymidine (*XIX*)

A. A suspension of 2′-deoxythymidine (2·4 g; 10 mmol) and benzoyl cyanide (2·9 g; 22 mmol) in acetonitrile (20 ml) was treated with triethylamine (0·5 ml) and the whole mixture stirred at room temperature to deposit crystals of compound *XIX*. After 2 h, the mixture was treated with ethanol (1 ml) and ether (100 ml) under continuous stirring. The precipitate was collected with suction, washed with ether, and recrystallised from ethanol to afford 4·5 g (a quantitative yield) of compound *XIX*, m.p. 195°C. For $C_{24}H_{22}N_2O_7$ (450·4) calculated: 64·00% C, 4·92% H, 6·22% N; found: 64·12% C, 4·85% H, 6·35% N. Optical rotation: $[\alpha]_D^{25}$ −36·6° (*c* 0·5; dimethylformamide).

B. A solution of fused lithium iodide (2·5 g) in dimethylformamide (10 ml) was treated successively at 100°C under stirring with compound *XVII* (1·35 g; 3 mmol) and 6M-HCl in dimethylformamide (1·5 ml). The mixture was stirred at 100°C for one hour, poured into water (200 ml), and extracted with three 50 ml portions of chloroform. The extract was washed with two 25 ml portions of 10% aqueous sodium thiosulfate and two 25 ml portions of water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was evaporated under diminished pressure, the residue coevaporated with three 25 ml portions of toluene at 40°C/0·1 Torr, and the final residue applied in methanol to two plates of silica gel. The elution was performed with a mixture of ethanol and chloroform (2 : 98). The ultraviolet-absorbing bands of compound *XVIII* (R_F 0·45) were eluted with methanol, the eluate evaporated under diminished pressure, and the crystalline residue purified by precipitation from ethanol (10 ml) with light petroleum (100 ml). The precipitate was collected with suction, washed with light petroleum, and dried under diminished pressure to afford 0·40 g (11%) of compound *XVIII*, homogeneous on thin-layer chromatography in the solvent system S_3. A mixture of this compound, tri-n-butyltin hydride (1·8 g), benzene (30 ml), and azabisisobutyronitrile (0·1 g) was refluxed for 30 minutes and then evaporated under diminished pressure. The residue was diluted with ethanol (2 ml) and precipitated with light petroleum (100 ml). The precipitate was collected with suction, washed with light petroleum, and crystallised from ethanol to afford 0·39 g (86%, referred to compound *XVIII*; 9·7%, referred to the starting compound *XVII*) of compound *XIX*, m.p. 195°C, undepressed on admixture with the specimen obtained by procedure *A*. Compound *XIX* was chromatographically homogeneous in the solvent systems S_3 and S_4 and identical with the specimen from paragraph *A*.

The author wishes to thank Professor F. Šorm for continued interest and encouragement, Dr J. Farkaš of this Institute and Dr J. Baschang, Geigy AG, Basel, Switzerland, for valuable discussions, and Dr W. Wechter, Upjohn Co., Kalamazoo, U.S.A., for providing the manuscript prior to publication and numerous physical data. Thanks are due also to Dr M. Masojidková for measurement and interpretation of NMR spectra, Dr I. Frič for measurement of CD spectra, and Dr I. Votruba for bacteriostatic tests. The excellent technical assistance of Mrs B. Kopecká is gratefully acknowledged.

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Translated by J. Pliml.