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SYNTHESIS OF NUCLEOSIDE AMINO ACIDS AND GLYCOSYL AMINO ACIDS

BY

ROBERT HUGH DODD

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Department of Chemistry

The University of British Columbia
2075 Wesbrook Place
Vancouver, Canada
V6T 1W5

Date August 24, 1979

ABSTRACT

The syntheses of glycos-3-yl and C-glycosyl α - and β -amino acid derivatives are described. The introduction of carbon-carbon linked substituents including β -alanine, at C-6 of uridine derivatives is also reported.

Knoevenagel condensation of ethyl cyanoacetate (263) with 1,2: 5,6-di-O-isopropylidene- α -D-ribo-hexofuranos-3-ulose (14) in N,N-dimethylformamide using ammonium acetate as the catalyst gave 3-C-[(R,S)-cyano(ethoxycarbonyl) methylene]-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (264) in 26% yield as well as a chromatographically inseparable mixture of 3-C-[(R,S)-cyano(ethoxycarbonyl) methylene]-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (265) and 3,3-C-bis[(RS, SS, RR)-cyano(ethoxycarbonyl) methyl]-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (266) in equal yields of 5%. Compound 264 was hydrogenated over platinum oxide in acetic anhydride to give in 96% yield 3-C-[(R,S)-acetamidomethyl(ethoxycarbonyl) methylene]-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (270). Dehydration of 264 with thionyl chloride in pyridine afforded 3-C-[(R,S)-cyano(ethoxycarbonyl) methylene]-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-erythro-hex-3-enofuranose (273). Compound 266 was isolated by reduction of 265 with sodium cyanoborohydride in methanol to give 3-deoxy-3-C-[(R,S)-cyano(ethoxycarbonyl) methylene]-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (268) followed by column chromatography on silica gel.

Reaction of 3-C-formyl-1,2:5,6-di-O-isopropylidene- α -D-

allofuranose (278) with sodium cyanide, ammonium carbonate and carbon dioxide gave in 53% yield 3-C-(2,4-diketo-tetrahydroimidazol-5-(R,S)-yl)-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (280). Treatment of 280 with barium hydroxide gave a 2:1 mixture of D-2 and L-2-(1,2:5,6-di-O-isopropylidene- α -D-allofuranos-3-yl) glycine (281), respectively, in a combined yield of 74%.

When ethyl cyanoacetate (263) was reacted with 2,5-anhydro-3,4,6-tri-O-benzoyl-D-allose (203) in *N,N*-dimethylformamide using ammonium acetate as catalyst, ethyl (E or Z)-4,7-anhydro-2-cyano-2,3,5-trideoxy-6,8-di-O-benzoyl-D-erythro-octon-2,4-dieneate (283) was produced in 31% yield. Hydrogenation of 283 over platinum oxide in acetic anhydride gave ethyl 4,7-anhydro-2-(R,S)-acetamidomethyl-6,8-di-O-benzoyl-2,3,5-trideoxy-4-(R,S)-D-erythro-D-octonate (284).

Reaction of 2,3-O-isopropylidene-5-O-trityl- β -D-ribofuranosyl chloride (210) with diethyl sodium phthalimidomalonate in *N,N*-dimethylformamide at 90° provided in 46% overall yield a 1:1 mixture of the α and β anomers of diethyl 2,3-O-isopropylidene-5-O-trityl-D-ribofuranosyl phthalimidomalonate (287 and 288, respectively). An attempt to unblock 287 and 288 with hydrochloric acid was unsuccessful.

Reaction of 2,4-di-*t*-butoxy-5-magnesiumbromopyrimidine (294) and acetone followed by treatment of the product with hydrochloric acid gave 5-(1-propen-2-yl)uracil (296) in 43% yield. The direct coupling of 294 with the glycosyl chloride 210 in the presence of catalytic iodo(phenyl)bis(triphenylphosphine) palladium (II) (298) was unsuccessful.

Addition of 2,2'-anhydro-1-(3-Q-acetyl-5-Q-trityl- β -D-arabinofuranosyl)uracil (308) to excess 2-lithio-1,3-dithiane (126) in tetrahydrofuran at -78° gave 2-(1,3-dithian-2-yl)-1-(5-Q-trityl- β -D-arabinofuranosyl)-4(1H)-pyrimidinone (309) and 2,2'-anhydro-5,6-dihydro-6-(S)-(1,3-dithian-2-yl)-1-(5-Q-trityl- β -D-arabinofuranosyl)uracil (310) in yields of 15 and 30%, respectively. Treatment of 309 with Raney nickel gave 2-methyl-1-(5-Q-trityl- β -D-arabinofuranosyl)-4(1H)-pyrimidinone (313) while hydrolysis of 309 in acid afforded 2-(1,3-dithian-2-yl)-4-pyrimidinone (314) and arabinose. Detritylation of 309 without glycosidic cleavage could only be effected by prior acetylation to 2-(1,3-dithian-2-yl)-1-(2,3-di-Q-acetyl-5-Q-trityl- β -D-arabinofuranosyl)-4(1H)-pyrimidinone (315) which, after treatment with acetic acid at room temperature followed by unblocking with sodium methoxide gave 2-(1,3-dithian-2-yl)-1- β -D-arabinofuranosyl)-4(1H)-pyrimidinone (317) in 45% yield. Hydrolysis of the dithioacetal moiety of 315 always led to glycosidic cleavage.

Treatment of compound 310 with Raney nickel gave 41% of 2,2'-anhydro-5,6-dihydro-6-R-methyl-5'-Q-trityluridine (318). Detritylation of 310 in refluxing acetic acid provided 10 and 90% yields of 5,6-dihydro-6-(S)-(1,3-dithian-2-yl)-1- β -D-arabinofuranosyluracil (319) and 3-[(S)-1-(1,3-dithian-2-yl)]propionamido- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (320), respectively. Acid hydrolysis of 319 afforded arabinose and 5,6-dihydro-6-(S)-(1,3-dithian-2-yl)uracil (321). Raney nickel treatment of 321 yielded the known 5,6-dihydro-6-methyluracil (322). When 319 was allowed to stand in water or

methanol for 4 days, quantitative conversion to 320 occurred. Dehydration of 320 with trifluoroacetic anhydride and pyridine afforded 3-[(S)-1-(1,3-dithian-2-yl)]cyanoethyl- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (328) in 77% yield. Similarly, 3-(R)-1-methylpropionamido- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (329), obtained by Raney nickel treatment of 320, gave 3-(R)-1-methylcyanoethyl- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (330). Treatment of 320 with excess p-nitrobenzoyl chloride in pyridine yielded 3-[(S)-1-(1,3-dithian-2-yl)]cyanoethyl-3',5'-di-O-p-nitrobenzoyl- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (333) which was converted by treatment with methyl iodide in dimethyl sulfoxide to 3-(S)-1-formylcyanoethyl-3',5'-di-O-p-nitrobenzoyl- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (335), characterized as its semicarbazone 336. An attempt to cyclize 328 with ammonia failed.

Addition of 5-bromo-2',3'-O-isopropylidene-5'-O-trityluridine (340) in pyridine to excess anion 126 in tetrahydrofuran at -78° gave 5,6-dihydro-6-(R)-(1,3-dithian-2-yl)-2',3'-O-isopropylidene-5'-O-trityluridine (341), 5-(S)-bromo-5,6-dihydro-6-(S)-(1,3-dithian-2-yl)-2',3'-O-isopropylidene-5'-O-trityluridine (342) and its 5-(R) isomer 343 in yields of 37, 35 and 10%, respectively. Desulfurization of 341 with Raney nickel afforded 5,6-dihydro-2',3'-O-isopropylidene-6-(S)-methyl-5'-O-trityluridine (346). Compound 341 was hydrolyzed in acid to give ribose and 5,6-dihydro-6-(R)-(1,3-dithian-2-yl)uracil (348). Treatment of 341 with methyl iodide in aqueous acetone gave a 30% yield of 5,6-dihydro-6-(R,S)-formyl-2',3'-O-isopropylidene-

5'-O-trityluridine (349), characterized as its semicarbazone 350.

Both 342 and 343 gave 341 upon brief treatment with Raney nickel. Both 342 and 343 gave 6-formyl-2',3'-O-isopropylidene-5'-O-trityluridine (351) in approximately 41% yield when treated with methyl iodide in aqueous acetone containing 10% dimethyl sulfoxide. A by-product, identified as 6-formyl-2',3'-O-isopropylidene-3-methyl-5'-O-trityluridine (353) was also formed. Reduction of 351 with sodium borohydride in ethanol afforded, after unblocking, 6-hydroxymethyluridine (356), characterized by its hydrolysis in acid to the known 6-hydroxymethyluracil (357). Knoevenagel condensation of a mixture of 351 and 353 with ethyl cyanoacetate (263) yielded 38% of E- or Z-6-[(2-carboethoxy-2-cyano)ethylidene]-2',3'-O-isopropylidene-5'-O-trityluridine (359) and 10% of its N-methyl derivative 360. Hydrogenation of 359 over platinum oxide in acetic anhydride followed by unblocking gave 6-[3-amino-2-(R or S)-carboxypropyl]uridine (363).

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I. OBJECTIVE

It has been repeatedly shown in the past two decades that various analogues of the common naturally-occurring nucleosides exhibit a wide range of biological properties. These modified nucleosides, obtained either from natural sources or by synthetic means, have often been found to be antifungal, antibiotic, antiviral or antitumour in their action.

Three classes of modified nucleosides can be distinguished: (1) nucleosides in which the ribosyl portion is altered by the incorporation of various groups, (2) C-nucleosides, in which a pyrimidine or purine base is linked to the sugar moiety by a carbon-carbon rather than a carbon-nitrogen bond, and (3) base-modified nucleosides, in which the common purine or pyrimidine moiety has been altered. Moreover, a feature common to many of the naturally-occurring biologically-active nucleoside analogues is the presence of an amino acid, usually linked by a peptidyl bond to the sugar moiety. Thus, puromycin (an antibiotic) and the polyoxins (fungicides) incorporate an α -amino acid while blasticidin S possesses a β -amino acid component.

The objective of the work described in this thesis is to develop general methods of attaching α - or β -amino acids to nucleosides or nucleoside precursors by carbon-carbon bonds. In the first part of this work, the synthesis of a 3-C- β -alanyl derivative of D-glucose by way of a Knoevenagel condensation of ethyl cyanoacetate with a 3-ketose was studied. An alternate method of making 3-C-glycylallofuranose using the Bucherer hydantoin procedure was also achieved.

The second part of this thesis is concerned with the

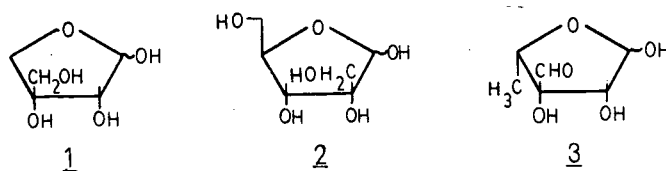
synthesis of functionalized precursors to C-nucleosides. The precursors envisioned were the C-glycosyl amino acid derivatives, the amino and carboxylic groups of the amino acid being potentially amenable to further derivatization. The two routes employed for the synthesis of such precursors were the condensation of ethyl cyanoacetate with a 2,5-anhydro-D-allose derivative and reaction of the anion of diethyl phthalimidomalonate with a ribosyl chloride derivative. A one-step synthesis of a C-nucleoside using a palladium catalyst was also attempted.

In the third part of this thesis, the reaction of 1,3-dithiane anion with uridine derivatives was investigated with a view to modifying the pyrimidine moiety of nucleosides. A general method of introducing substituents, including β -alanine, at C-6 of uridine was thus developed and some of the resulting analogues were evaluated for biological activity.

II. INTRODUCTION

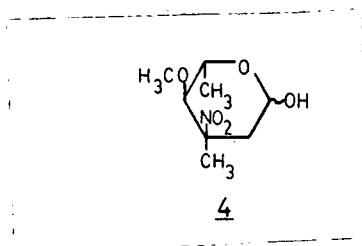
1. Branched-Chain Sugars

A branched-chain sugar is a carbohydrate in which a hydrogen or hydroxyl group is replaced by an organic group through a carbon-carbon bond thereby giving rise to branching of the carbohydrate skeleton. The first such branched-chain sugar, apiose (1) was isolated from parsley by Vongerichten¹ in 1901 but its structure was only elucidated thirty years later by O. Th. Schmidt.² A second branched-chain sugar, hamamelose³, was discovered in the hydrolysate of the tannin of Hamamelis virginiana by Fischer and Freudenberg in 1912 and its structure was later shown to be 2-C-hydroxymethyl-D-ribose⁴ (2). Interest in these anomalous sugars lay dormant until branched-chain sugars were discovered to be vital glycosidic components⁵ in the structure of antibiotics.⁶⁻¹¹ For instance, streptose¹² (3) was found as a constituent of streptomycin. Branched-chain sugars have now been isolated from higher plants¹³⁻¹⁴ from cell wall polysaccharides¹⁴⁻¹⁵ and even from man.¹⁶ However, the discovery that nucleosides of branched-chain sugars can have cytostatic and virostatic activity has stimulated interest in the synthesis of such compounds.¹⁷⁻¹⁹



Branched-chain sugars have been divided into two classes.²⁰ Those in which branching occurs by substitution of a carbon-

linked hydrogen by a group R belong to the Type A classification while substitution of a hydroxyl group by R gives rise to Type B. The latter are often referred to as "deoxy" sugars. Both D-apiose²¹ (1) and D-hamamelose²⁰ (2) are examples of Type A sugars. Type B sugars are exemplified by L-evernitrose²²⁻²³ (4).

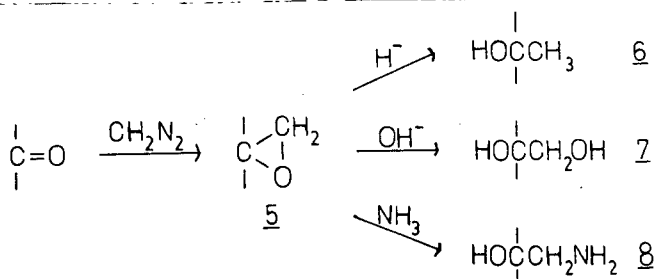


The synthesis of branched-chain sugars has been the subject of several reviews^{7-8 24} and so the following discussion will summarize the more important methods of synthesizing Type A, Type B, and the more specialized glycosyl amino acid sugars. The use of 1,3-dithianes to construct branched-chains will be discussed in a separate section (see Section 3.3).

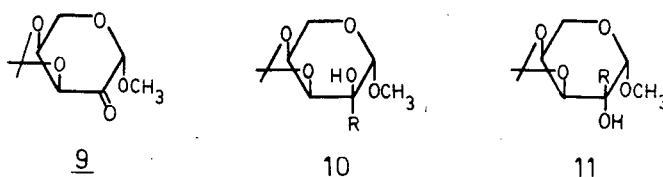
1.1 Synthesis of Type A Sugars (R-C-OH).

Keto sugars^{8 25} have been widely used as starting material for the synthesis of Type A carbohydrates. For instance, addition of diazomethane to a keto sugar results in the formation of an epoxide 5 which can be reduced to the C-methyl compound 6, hydrolyzed to the C-hydroxymethyl compound (7) or converted by ammonolysis to the C-aminomethyl compound (8).²⁶⁻²⁷

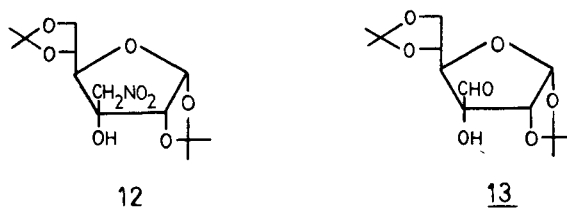
Addition of organolithium and organomagnesium reagents to keto sugars can occur in a sterically complementary manner, as was shown for the 2-ketose 9. Reaction of 9 with organolithium compounds gave the L-ribo branched-chain sugar (10) whereas organomagnesium reagents afforded mainly the L-arabino sugars



(11).²⁸ However, changing the blocking groups of the reacting keto sugar has been shown to influence the stereoselectivity of these reactions.²⁹



The base-catalyzed condensation of nitromethane with keto sugars yields branched-chain nitromethyl derivatives,³⁰⁻³² the nitro group of which can be reduced to give aminomethyl sugars of Type A. The nitromethyl group of 12 has also been oxidized with potassium permanganate to the 3-aldehyde³³ (13), an analogue of streptose (3). Again, the type of blocking groups



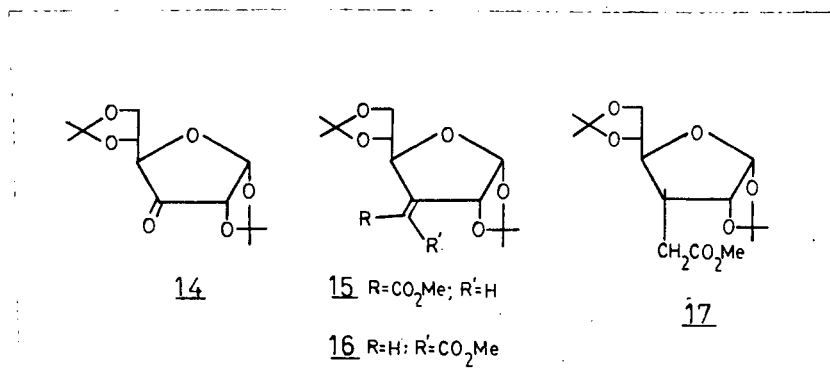
used on the keto sugar affects the stereochemical course of nitromethane addition.³²

Other methods which have been employed to synthesize Type A sugars from ketoses have included the nucleophilic addition of C-methyl groups using dimethylsulfoxonium methylide³⁴ and condensation with sodium cyanide³⁵ and acetonitrile³⁶ to give cyano and cyanomethyl compounds respectively. Also,

photoamidation of a disubstituted 3-enofuranose affords the 3-C-carbamoyl derivative.³⁷

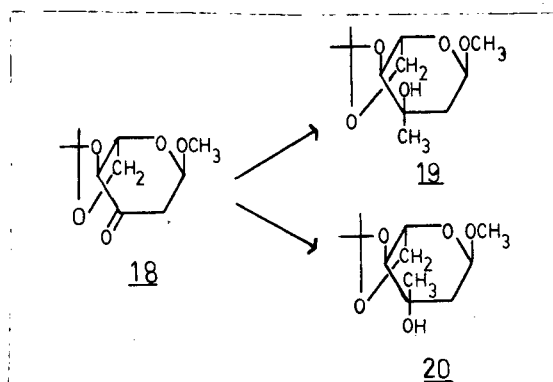
1.2 Synthesis of Type B Sugars ($R-\overset{|}{\underset{|}{\text{C}}}-H$).

Application of the Wittig reaction to keto sugars has allowed ready access to functionalized branched-chain sugars of Type B.³⁸⁻⁴⁴ It was first employed by Rosenthal and Nguyen³⁸ who reacted the 3-ketose 14 with methyl dimethoxyphosphonoacetate and potassium tert-butoxide to give the cis and trans branched-chain sugars 15 and 16. Catalytic reduction of this mixture gave exclusively the allo methoxycarbonylmethyl branched-chain sugar 17.

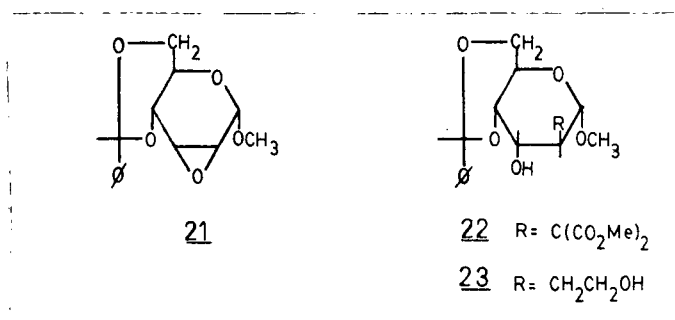


The Wittig reaction has also been used to synthesize Type A sugars not available by the methods previously discussed. Thus, whereas reaction of ketose 18 with methylmagnesium iodide gave the L-ribo branched-chain sugar 19,⁴⁵ treatment with triphenylmethylenephosphorane and then with mercuric acetate and sodium borohydride gave the L-arabino analogue of 19 (20).⁴⁶

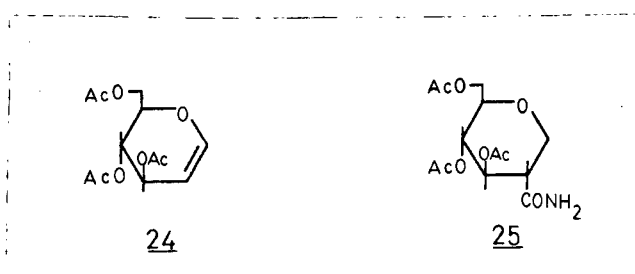
Type B sugars can also be obtained by the addition of nucleophiles to anhydro sugars.⁴⁷⁻⁴⁹ Trans-diaxial opening of the epoxide is generally observed.⁴⁸⁻⁵⁰ As an example, reaction of the 2,3-anhydro sugar 21 with sodio diethyl malonate gave the 2-C-branched-chain sugar 22 which could be reduced with lithium



aluminum hydride to provide the hydroxyethyl derivative (23)⁵¹.



Unsaturated sugars have found use as precursors to "deoxy" branched-chain carbohydrates by way of the oxo reaction, the application of which to carbohydrates has been reviewed by Rosenthal.⁵² The reaction allows introduction of a formyl group at one end of the unsaturated bond.⁵³ Also, unsaturated sugars undergo photoamidation reactions by which a carbamoyl branched-chain can be added. Thus, irradiation of a solution of the glycal 24 in formamide gave the C-2 addition product 25 together with products arising from photoamidation at C-1.⁵⁴



1.3 Synthesis of Glycosyl† Amino Acids.

†Used in the extended sense.

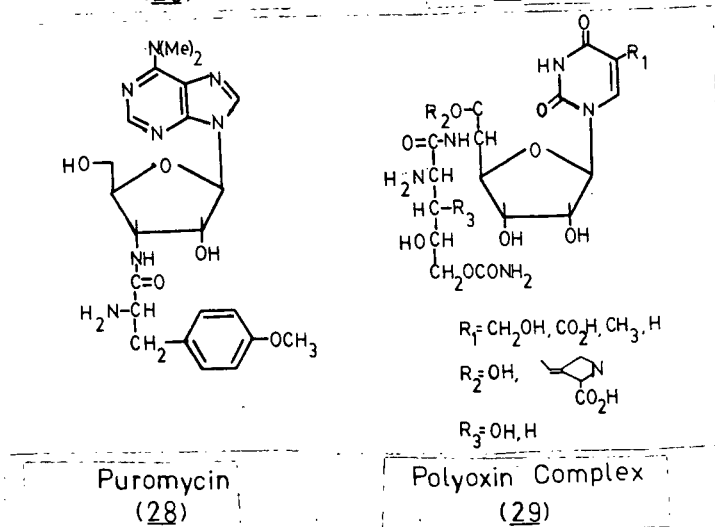
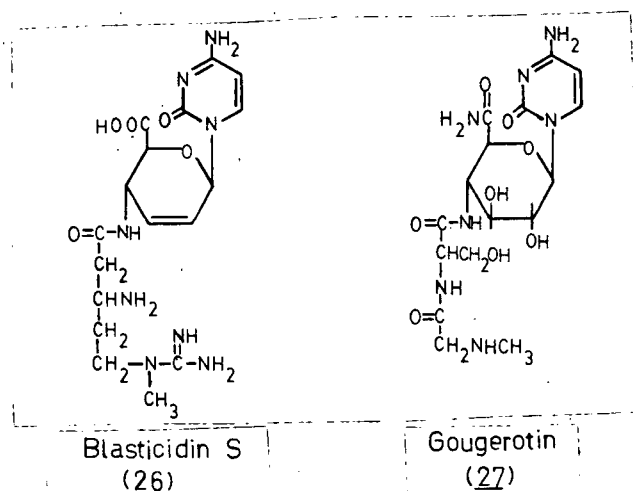
1.3.1 α -Amino Acids.

The importance of nucleosides as components of many antibiotics has been acknowledged.¹⁷⁻¹⁹ In particular, nucleosides having peptide linkages and amino acid groups attached to their carbohydrate moieties have evinced antibiotic properties. Among the naturally occurring compounds of this type are blasticidin S (26), gougerotin (27), puromycin (28) and the polyoxins (29); all except the latter inhibit protein synthesis¹⁹. The polyoxins, of which there are twelve variations and whose structures were elucidated by Isono⁵⁵, are mainly antifungal in their action and have been used to control sheath blight in rice plants. The polyoxins have also shown effectiveness in inhibiting tobacco mosaic virus.⁵⁶ They have no activity towards animals, fish or plants.

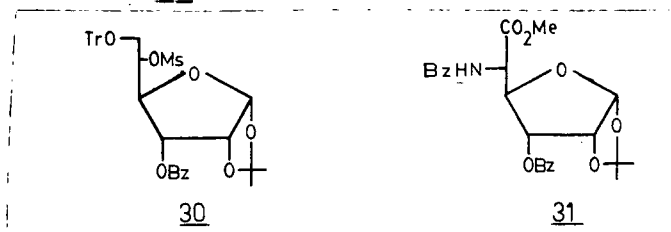
The mode of action of the polyoxins probably involves inhibition of glucosamine uptake⁵⁷ thereby⁵⁸ interfering with cell-wall chitin biosynthesis.^{18a}

Whereas the chemical synthesis of analogues of blasticidin S (26), gougerotin (27) and puromycin (28) involves attachment of an amino acid functionality to a carbohydrate through a nitrogen atom⁵⁹⁻⁶⁴, the sugar components of the polyoxins are linked directly to the α -carbon of the amino acid. Such units are referred to specifically as glycosyl amino acids.

Most syntheses of glycosyl amino acids reported to date have utilized the displacement of a methanesulfonyloxy⁶⁵⁻⁶⁷ or a toluenesulfonyloxy⁶⁸⁻⁷⁰ group with sodium azide followed by reduction of the resulting azide to the amine. Thus, in the first reported synthesis of an analogue of a polyoxin sugar

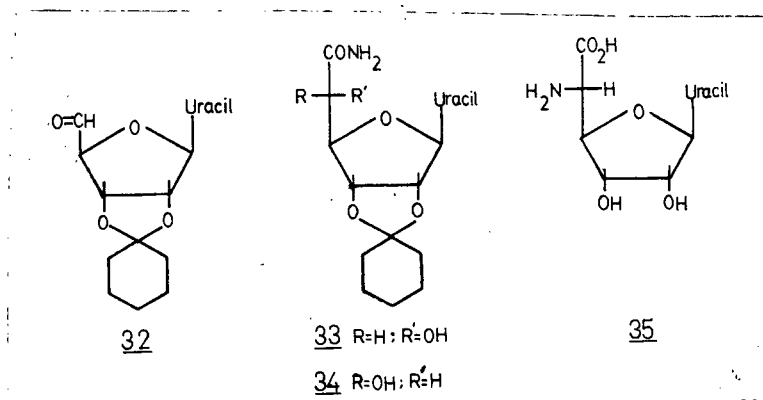


moiety, Naka and co-workers⁶⁵ used the azide displacement of the 5-sulfonyloxy group of the hexofuranose 30 which after catalytic reduction of the azide followed by permanganate oxidation of the unblocked 6-hydroxyl group gave the 5-amino-5-deoxy allofuranuronic acid 31.



A similar route beginning with the uridine analogue of 30 was used by Emoto⁶⁷ to construct the basic polyoxin skeleton. The latter was also obtained by Moffatt and co-workers⁶⁶ who started with the 5'-aldehyde (32) the reaction of which with

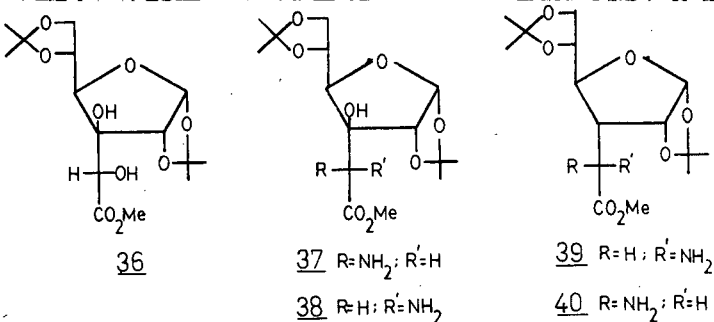
sodium cyanide in aqueous methanolic potassium carbonate and hydrogen peroxide yielded the epimeric C-5 hydroxy amides 33 and 34. Mesylation of the free hydroxyl group of 33 followed by azide displacement of the sulfonate, hydrolysis of the amide and reduction of the azide gave the polyoxin analogue 35.



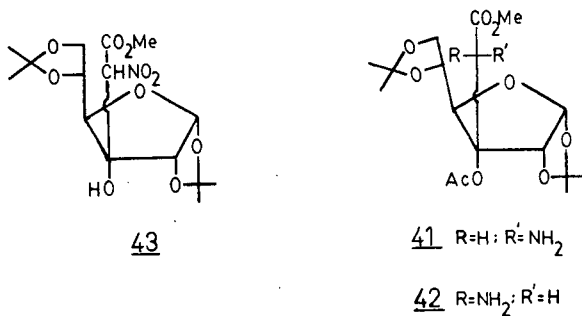
The synthesis of glycosyl amino acids with branching at C-3 has been pursued mainly by Rosenthal and coworkers.⁶⁸⁻⁷¹ Beginning with the α, β -dihydroxy ester 36, obtained by permanganate or osmium tetroxide oxidation of the double-bond of 16, monotosylation of the exocyclic hydroxyl group was achieved whence conversion to the amine by the sequence just discussed yielded, after unblocking, the D-amino acid sugar derivative (37).⁷¹ Similar treatment of the cis-isomer 15 gave the L-amino acid (38)⁷¹. The 3-deoxy analogue of 38 (39) was obtained by selective acetylation of the α -hydroxy group of the dihydroxy ester 36 followed by stereoselective dehydration with thionyl chloride and pyridine and subsequent conversion of the free α -hydroxy group to the amine⁶⁸ as before. Similarly, compound 15 afforded the expected 3-deoxy-D-amino acid sugar (40).⁷⁰

The D - gluco

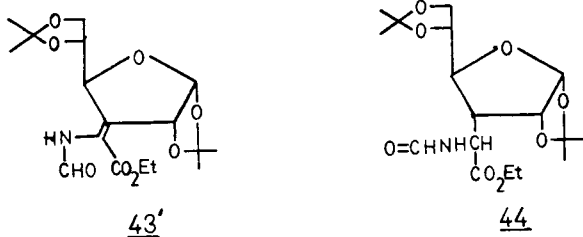
isomers of 37 (41 and 42 respectively)



have been synthesized by condensation of methyl nitroacetate with the 3-ketose 14 to give 43, followed by reduction of the nitro group of the acetylated products.⁷²

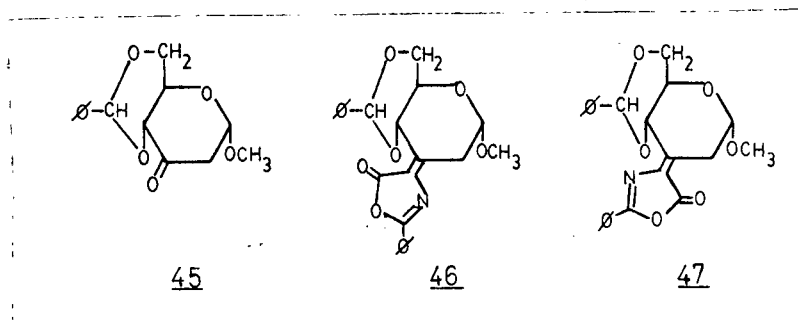


A blocked D-amino acid sugar (44) was generated when Jordaan and Brink^{73 74} reduced the product (43) obtained from the reaction of ethyl isocyanoacetate with the ketose 14. The sequence has also been applied by them to 2-keto sugars.⁷⁵

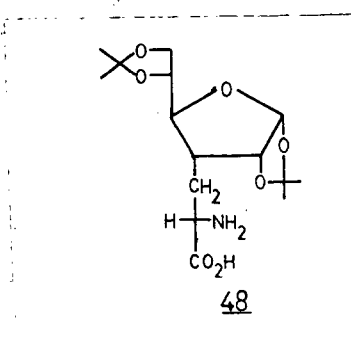


The 2-deoxy-3-ketose 45 has served as starting material for the synthesis of hexopyranosyl glycine derivatives via the azlactone condensation.⁷⁶ The E and Z oxazolinones (46 and 47) were isolated from the reaction mixture both of which were subjected to methanolysis followed by catalytic reduction to give the arabino and the ribo branched-chain sugars,

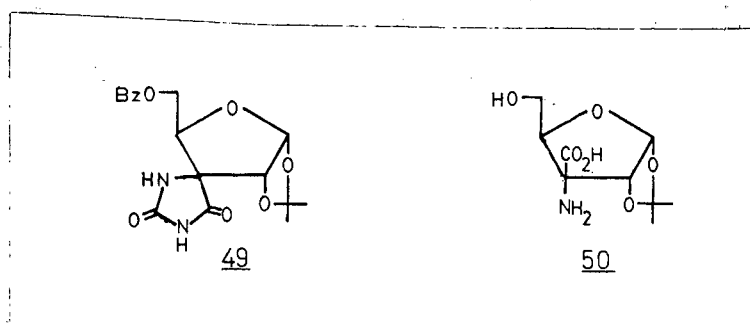
respectively. Both compounds were assigned the D-glycine configuration.



In addition to glycine, the terminal carbon of α -L-alanine has been attached to a furanose to give 48.⁷⁷ The synthesis, based on a method reported by Ogura and Tsuchihashi⁷⁸, proceeds from the addition of the anion of methyl(methylthio)methyl sulfoxide to the nitrile functionality of 3-C-cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose.



The Bucherer hydantoin synthesis⁷⁹ of glycine derivatives was used by Umezawa⁸⁰ to prepare 49 from the corresponding ketose. Hydrolysis of 49 with base then afforded the novel 3-amino-3-C-carboxy-3-deoxy sugar 50.

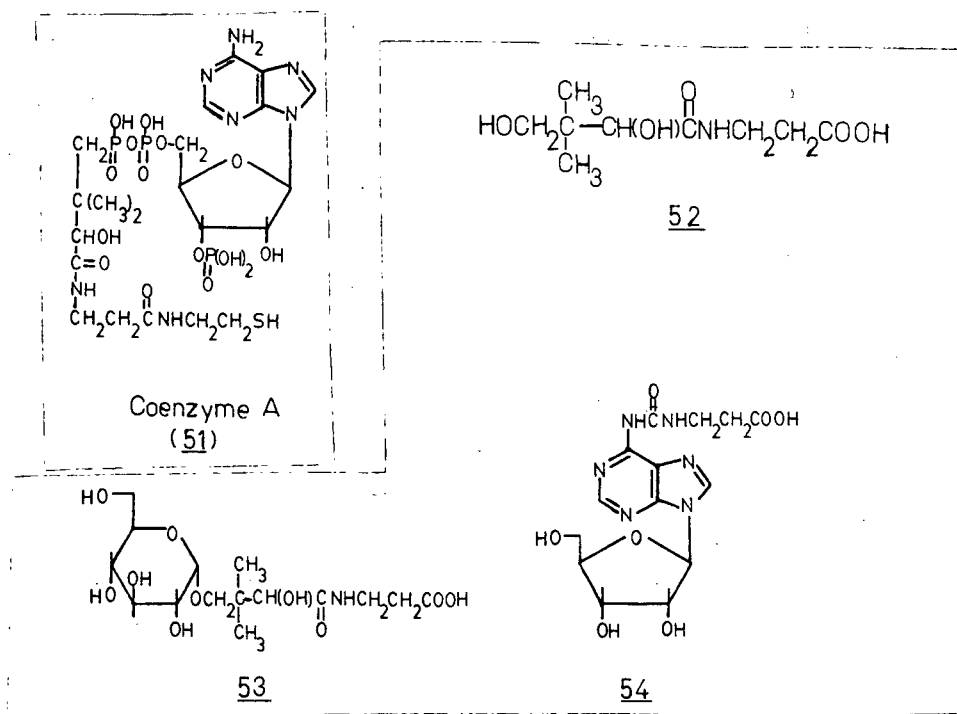


1.3.2 β -Alanine

β -Amino acids, in which the amino and carboxylic functions are separated by two carbons, are much more rarely found as components of naturally-occurring saccharides and nucleosides than are α -amino acids. Coenzyme A (51), an essential cofactor for acetylation reactions in the liver and brain^{81 82} and necessary in the biosynthesis⁸³⁻⁸⁴ and biodegradation⁸⁵⁻⁸⁶ of fatty acids, the metabolism of erythrocytes⁸⁷⁻⁸⁸ and the phosphorylation⁸⁹⁻⁹⁰ of various biologically important molecules, incorporates β -alanine as part of the diphosphate-linked side-chain at C-5'. The structure of coenzyme A was established by a series of selective enzymic degradations⁹¹⁻⁹³ and by total synthesis⁹⁴⁻⁹⁶

Pantothenic acid (52) is a β -alanyl-containing vitamin (B3)⁹⁷ which has also been obtained naturally as an α -D-glucoside (53) possessing microbial activity.⁹⁸⁻¹⁰⁰

Recently, the 6-ureido β -alanine purine nucleoside 54 was synthesized¹⁰¹ and found to be an inhibitor of adenosine



kinase.¹⁰²

Blasticidin S (26) also incorporates a β -alanine residue in its side-chain.

2. Synthesis of Amino Acids

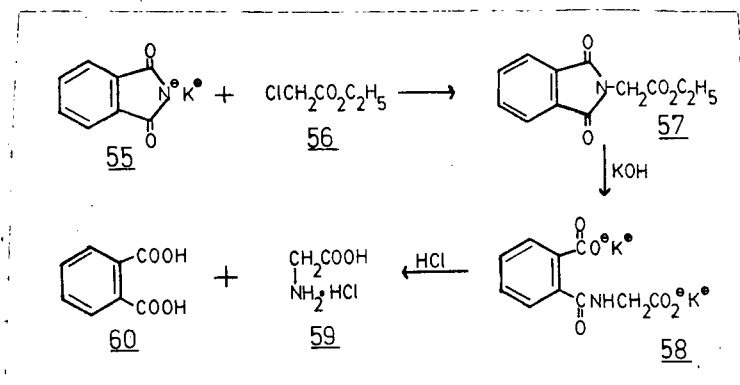
The first laboratory synthesis of a naturally-occurring amino acid dates back to 1850¹⁰³ when Strecker produced alanine from acetaldehyde using the cyanohydrin method. Procedures for the synthesis of other amino acids, both natural and unnatural, were gradually taken up by Erlenmeyer¹⁰⁴, Fischer¹⁰⁵, Sørensen¹⁰⁶ and others. Their resulting methodologies, or variations thereon, were, until twenty years ago, the standard procedures for the preparation of amino acids. Since then, a number of synthetic methods have been developed, notably alkylations using the trianion of hippuric acid¹⁰⁷ or the anion of methyl methylthiomethyl sulfoxide⁷⁸, amidoalkylations with glyoxylic acid¹⁰⁸, condensations of carbonyl compounds with

carboxylic acid, amine and isocyanide¹⁰⁹⁻¹¹², the use of trihalomethyl carbanions as nitrile equivalents¹¹³ and reactions of copper glycinate.¹¹⁴

The application of any of the classical syntheses of amino acids to the production of glycosyl amino acids (see Section 1.3) has been lacking. The following then is a brief discussion of three methods used in the present work to produce glycosyl amino acids or their precursors.

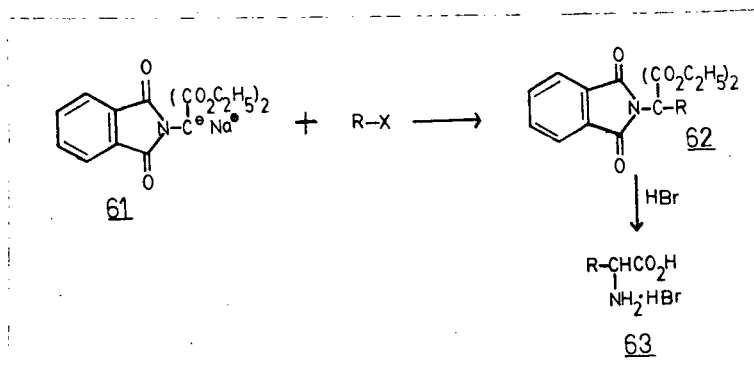
2.1 The Sørensen Synthesis of Amino Acids

The first synthesis of glycine, developed by Goedeckemeyer¹¹⁵ in 1888, employed the reaction of potassium phthalimide (55) with ethyl chloroacetate (56) to give ethyl phthalylglycinate (57) which was then hydrolyzed with potassium hydroxide to the di-potassium salt (58). Acid treatment of the latter then gave glycine hydrochloride (59) and phthalic acid (60).



This reaction sequence was then developed a year later by Gabriel¹¹⁶ as a general procedure for the synthesis of amines from various organic halides, a reaction which now bears his name. It was then fifteen years before Sørensen^{106 117-120} was able to adapt the Gabriel synthesis to make amino acids. The

general scheme involved reaction of the sodium salt of ethyl phthalimidomalonate (61) with an appropriate organic halide to give the monoalkyl (or aryl) phthalimidomalononic ester (62) from which the amino acid (63) was liberated by acid treatment.

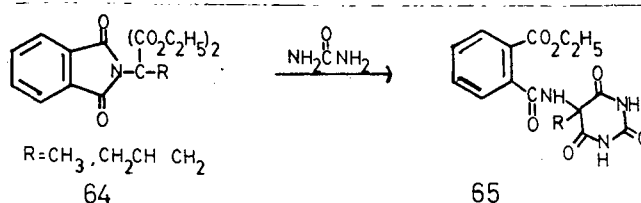


Sørensen thus prepared phenylalanine¹¹⁷, proline¹¹⁸, ornithine¹¹⁷ and α-aminoadipic acid¹¹⁸ by reaction of 61 with benzyl chloride, trimethylene bromide, γ-bromopropylphthalimide and γ-chlorobutyronitrile, respectively. In later years, the Sørensen method was used to synthesize tyrosine¹²¹ from anisyl bromide, serine¹²² from monochlorodimethyl ether, methionine¹²³ from β-chloroethylmethyl sulfide, and aspartic acid¹²⁴ from chloroacetic ester. Some lack of generality in the Sørensen procedure was observed by Dunn and Smart¹²⁴; attempts to form glutamic acid from condensation of 55 with ethylene bromide, ethylene chloride, β-chloropropionitrile or β-chloropropionic ester failed to give any stable products.

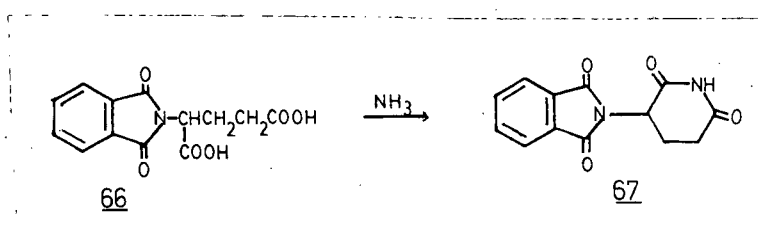
Only minor innovations have been made in the basic Sørensen synthesis over the years. A more efficient method of generating the sodium salt 61 from ethyl phthalimidomalonate has been developed based on the use of toluene rather than ethanol as the reaction solvent.¹²⁴ As well, generation of the amino acid 63

from 62 has been facilitated by use of hydrobromic acid or hydrazine¹²⁵, the latter giving rise to phthalazine rather than phthalic acid (60) as the reaction co-product.

More modern applications of the Sørensen method include the production of tropyglycine,¹²⁶ a potentially therapeutic analogue of phenylalanine, from tropylium perchlorate and the synthesis of 5-alkyl-5-benzamidobarbiturates¹²⁷ (65) from diethyl- α -alkyl- α -phthalimidomalonate (64) and urea in the presence of sodium ethoxide. Cleavage of the phthalimide ring was observed in the latter reaction. Thalidomide (67) (N-(2,6-

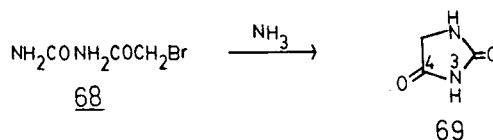


dioxo-3-piperidyl) phthalimide)¹²⁸ was prepared by the action of ammonia on N-phthalylglutamic acid (66).



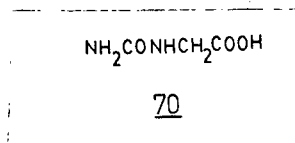
2.2 The Hydantoin Synthesis of Amino Acids.

Hydantoins (69) which are 2,4-diketotetrahydroimidazoles, were first synthesized by Baeyer¹²⁹ when he heated bromoacetylurea (68) with ammonia.

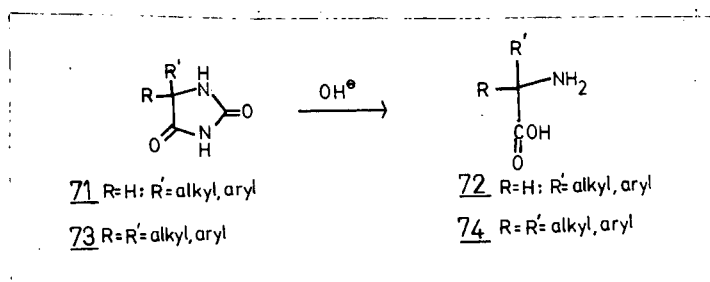


The value of hydantoin (69) in amino acid synthesis is

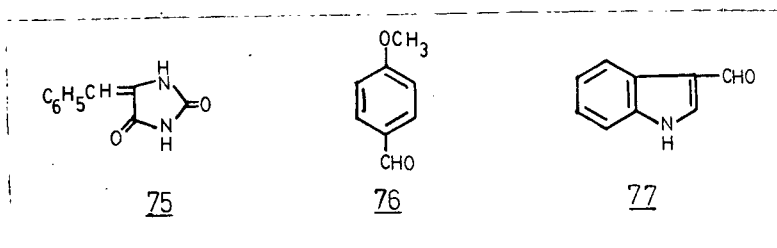
apparent when it is considered as a masked form of glycine; hydrolysis¹³⁰, usually with aqueous barium hydroxide, first gives hydantoic acid (70) as an intermediate via cleavage of the 3,4-bond. Further reaction then gives glycine as the final



product. By substituting one of the acidic¹³¹⁻¹³³ protons at the 5-position with an alkyl or aryl group (71) a general method of forming various α -amino acids (72) is achieved. Ingold and co-workers¹³⁰ have shown that the ease of hydrolysis of the hydantoin ring (71) depends on the nature of the 5-substituents.

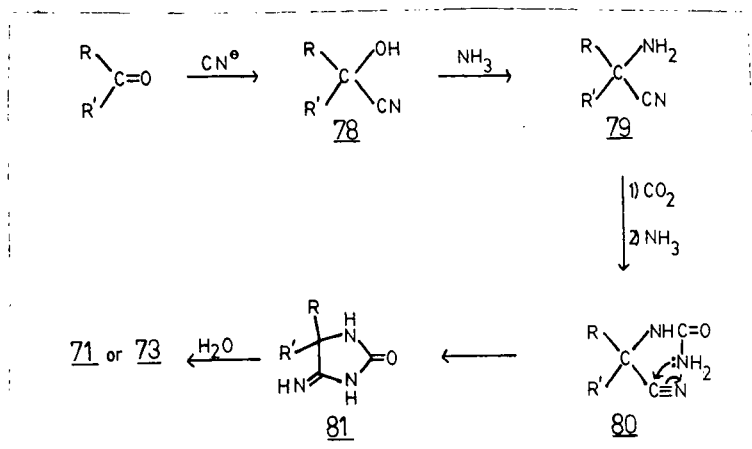


The method was used early in this century to prepare aryl-substituted α -amino acids from aromatic aldehydes. Thus, reaction¹³⁴ of benzaldehyde with hydantoin (69) under basic conditions afforded the unsaturated condensation product 75 which was reduced and hydrolyzed to give phenylalanine (72, R'=CH₂ C₆H₅). Similarly, tyrosine¹³⁵ and tryptophane¹³⁶ were obtained from anisaldehyde (76) and β -indole aldehyde (77).



Though many routes to 5-substituted and 5,5-disubstituted

hydantoins (71 and 73, respectively) have been developed over the years¹³⁷, the synthetically simplest and most successful is that introduced by Berg¹³⁸ and developed by Bucherer.¹³⁹⁻¹⁴⁰ In this procedure, an aldehyde or ketone is heated in alcohol with potassium cyanide and ammonium carbonate giving directly the hydantoin 71 (in the case of an aldehyde) or 73 (for a ketone). The mechanism as proposed by Bucherer though never experimentally verified involves initial formation of the cyanohydrin 78 from the carbonyl compound followed by reaction with ammonia (generated, together with carbon dioxide, from the ammonium carbonate) to give the amino-nitrile 79. Reaction of the latter with carbon dioxide and ammonia then yields the N-substituted carbamic acid 80 which then cyclizes to the imine 81. Hydrolysis of 81 affords the hydantoin 71 (or 73).



By this method, Bucherer was able to synthesize a variety of new amino acids. The generality of the original Bucherer hydantoin synthesis was later markedly enhanced by the use of acetamide as solvent¹⁴¹ and by conducting the reaction under several atmospheres of carbon dioxide.¹⁴²

Hydantoins that are disubstituted at the 5-position display

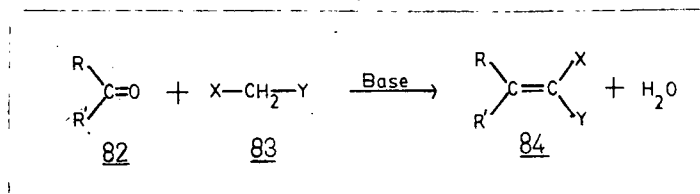
hypnotic properties comparable to the structurally related barbiturates and moreover, are used as anticonvulsants in the treatment of epilepsy.^{137 143}

In the carbohydrate field, the Bucherer synthesis has been applied by Umezawa and co-workers to prepare 3-amino-3-C-carboxy-3-deoxy sugars^{80 144} (50) (see Section 1.3.1) and their adenine nucleosides.⁸⁰ No biological properties of this compound were reported.

2.3 The Knoevenagel Condensation: Access to β -Amino Acids.

2.3.1 - Definition and Mechanism.

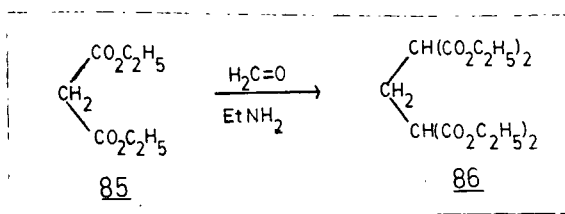
The Knoevenagel condensation¹⁴⁵ may be defined as the reaction between an aldehyde or a ketone (82) and a compound containing an active methylene group (83), catalyzed by an organic base, ammonia or their salts. The usual product is the unsaturated addition compound 84. The methylene group of 83 is



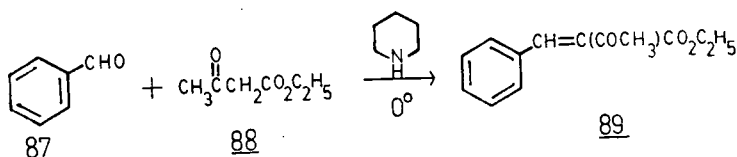
activated by the presence of electron-withdrawing groups (X, Y), such as NO_2 , quaternary pyridinium, CN, COR, CONHR, CO_2R , SO_2 , S, or Ar. Generally two such groups are required for activation of 83 unless a nitro or quaternized pyridine group is present. The reactivity of 83 decreases in the order $\text{NO}_2 > \text{CN} > \text{COCH}_3 > \text{COC}_6\text{H}_5 > \text{CO}_2\text{C}_2\text{H}_5 > \text{C}_6\text{H}_5$.¹⁴⁶ It is also generally accepted that at least a catalytic amount of acid, in addition to the nitrogenous base, is required for successful

condensation¹⁴⁷⁻¹⁴⁹, although too much acid tends to suppress the reaction.¹⁵⁰⁻¹⁵³ The basic catalysts generally employed are ammonia, primary or secondary amines, pyridine or ammonium salts such as ammonium acetate. Ion-exchange resins,^{154 155} metal fluorides¹⁵⁶⁻¹⁵⁷ and potassium cyanide¹⁵⁸ have also been used as catalysts for the Knoevenagel condensation.

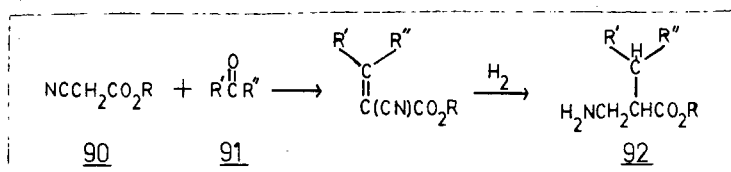
In his original investigation, Knoevenagel condensed formaldehyde with diethyl malonate (85), using ethylamine as base, to give the bis product 86.¹⁵⁹ However, subsequent work showed that condensations leading to unsaturated compounds such as 84 were generally applicable.¹⁶⁰ Thus, benzaldehyde (87) and ethyl acetoacetate (88) reacted at freezing temperatures in the



presence of piperidine to give ethyl benzylideneacetoacetate (89).



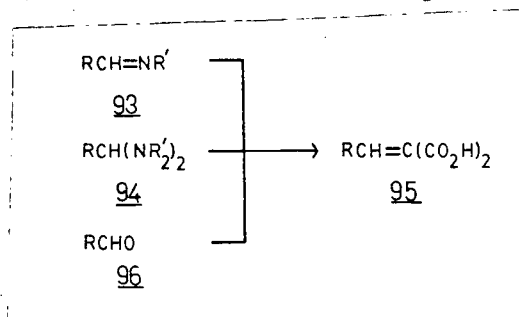
The Knoevenagel condensation of active methylene compounds such as nitromethane, methyl nitroacetate and ethyl isocyanoacetate with ketoses as a route to branched-chain sugars has been discussed (see Sections 1.1 and 1.3.1). The Knoevenagel procedure also provides access to substituted β -alanine derivatives (92) by condensation of cyanoacetic esters(90) with appropriate ketones or aldehydes (91), followed by reduction of the unsaturated bonds.¹⁶¹⁻¹⁶²



The following then is a discussion of the proposed mechanisms of the Knoevenagel condensation, the particular use of cyanoacetic esters in this reaction and applications of the latter to the field of carbohydrates.

2.3.1.1 The Knoevenagel Mechanism.

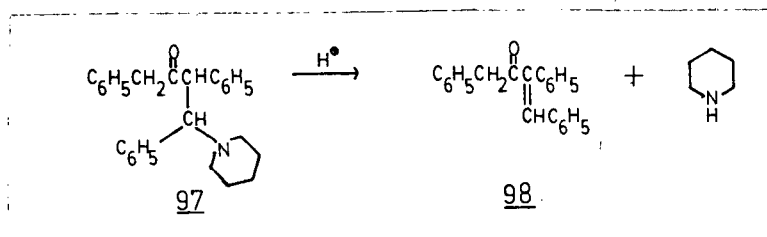
Knoevenagel observed, in a series of experiments, that both a Schiff base (93) and a bis-(dialkylamino) compound (94) could react with malonic acid to give the same alkylidene product (95), this product, in turn, being identical to that obtained by reaction of malonic acid with the corresponding aldehyde (96) under catalysis with ammonia, a primary amine or a secondary amine.¹⁶³⁻¹⁶⁴ This verified his theory that the role of the



amine was to react with the aldehyde to form the Schiff base 93 (in the case of ammonia or a primary amine) or compound 94 (in the case of a secondary amine), these intermediates then reacting with the active methylene component to yield 95.

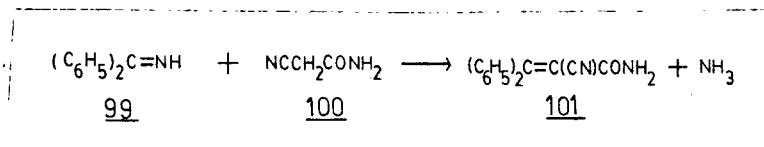
Support for this proposal came mainly from the isolation of nitrogen-containing compounds from reactions conducted under Knoevenagel conditions. Moreover, further treatment of these

intermediates gave the typical Knoevenagel condensation products. For example, Diltthey and Stallman¹⁶⁵⁻¹⁶⁶ were able to isolate the piperidide 97 from the reaction of benzaldehyde (87), dibenzylketone, and piperidine. Treatment of 97 with acid



then gave the unsaturated dibenzyl ketone 98 and piperidine. The possibility that 97 formed by addition of piperidine to the initially formed unsaturated compound 98 was discounted, by the same investigators.¹⁶⁷

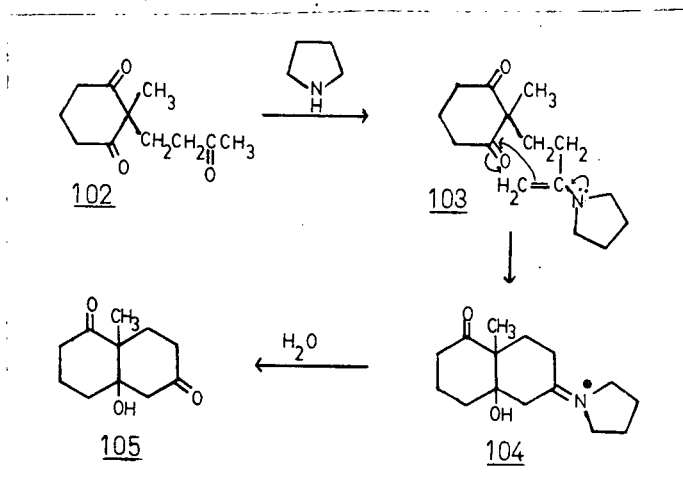
A more recent study by Charles¹⁶⁸ also indicated that imines and N-substituted imines could be used as starting materials for Knoevenagel-type condensations with active methylene compounds. Thus, reaction of benzophenone imine (99) with cyanoacetamide (100) gave, without the use of catalyst, compound 101.



In addition, the Knoevenagel mechanism has received support from the results of reaction rate studies in which ammonia or a primary amine was used as catalyst; aldehydes tending to form the most stable Schiff bases were also those which formed Knoevenagel condensation products the most slowly.¹⁶⁹

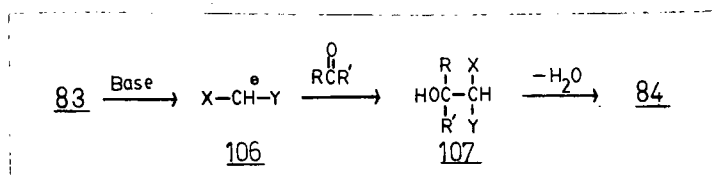
In cases where the active methylene compound has an enolizable ketone, a modification of the Knoevenagel mechanism has been invoked wherein an enamine is first formed which serves

as the nucleophile in attack of another carbonyl group.¹⁷⁰⁻¹⁷¹ For instance, the intramolecular cyclization of compound 102 is believed to proceed by initial reaction with the catalytic pyrrolidine to give the enamine 103 which then further reacts to give the charged imine 104. Hydrolysis of 104 then generates the ketone 105.



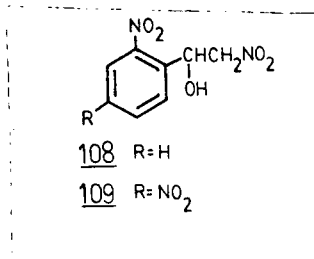
2.3.1.2 The Hann and Lapworth Mechanism

The observation by Verley¹⁷² and Doebner¹⁷³ that pyridine, a tertiary amine, could be used to effectively catalyze Knoevenagel condensations led Hann and Lapworth¹⁷⁴ to propose that the function of the base in these reactions was to remove a proton from the active methylene compound to give an anion (106) which then added to the carbonyl compound. The resulting alcohol (107) could then dehydrate to form the usual condensation product (84).

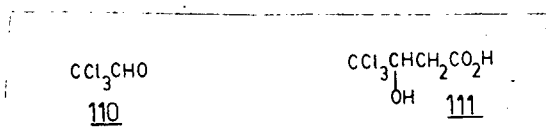


Evidence for this mechanism has come from the isolation of the hydroxy intermediates 107. Thus, reaction of nitromethane

with 2-nitrobenzaldehyde and 2,4-dinitrobenzaldehyde gave compounds 108 and 109, respectively.¹⁷⁵ Similarly,



trichloroacetaldehyde (110) and malonic acid yielded the β -hydroxy acid 111, decarboxylation occurring spontaneously.¹⁷⁶



Kinetic studies of the Knoevenagel reaction showed that, in general, added acid decreased the rate of reaction while added salts such as lithium chloride increased the rate, inferring that ionization of the active methylene compound (83) was the rate-determining step.¹⁵⁰⁻¹⁵³ The order of reactivity of active methylene compounds was determined to be $\text{CH}_2(\text{CN})_2 > \text{CH}_2(\text{CN})\text{CO}_2\text{C}_2\text{H}_5 > \text{CH}_2(\text{CN})\text{CONH}_2 > \text{CH}_2(\text{CO}_2\text{C}_2\text{H}_5)_2$.¹⁵³ The dissociation constants of these compounds follow a similar trend.

A modified Hann and Lapworth mechanism has been suggested in which protonated amines are the active catalysts in the Knoevenagel condensation.^{169 177-178} The introduction by Cope of ammonium acetate and other amine acetates as effective catalysts has reinforced this possibility.¹⁴⁷⁻¹⁴⁸

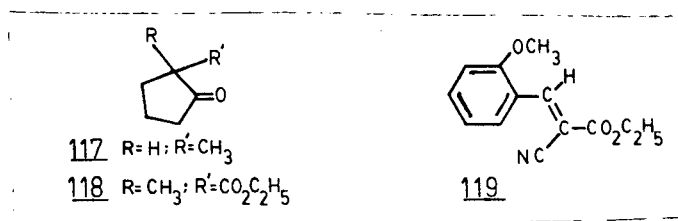
2.3.2 Knoevenagel Condensations with Cyanoacetic Esters.

2.3.2.1 Non-Carbohydrate Applications.

Cyanoacetic esters generally condense with aldehydes and

condensation occurred readily, while with 118, in which there are two α -substituents, there was essentially no reaction.¹⁸⁴

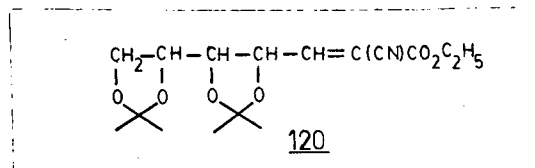
Steric considerations also enter into the explanations of the observed stereoselectivity of the condensations of cyanoacetic esters with aldehydes.¹⁸⁵ To illustrate, 2-methoxybenzaldehyde reacts with ethyl cyanoacetate to give exclusively the trans product 119,¹⁸⁶ a geometry which allows the greatest distance between the bulky phenyl and ester groups.



No such stereoselectivity is generally seen in analogous condensations with ketones.¹⁸⁷⁻¹⁸⁹

2.3.2.2. Applications to Carbohydrates.

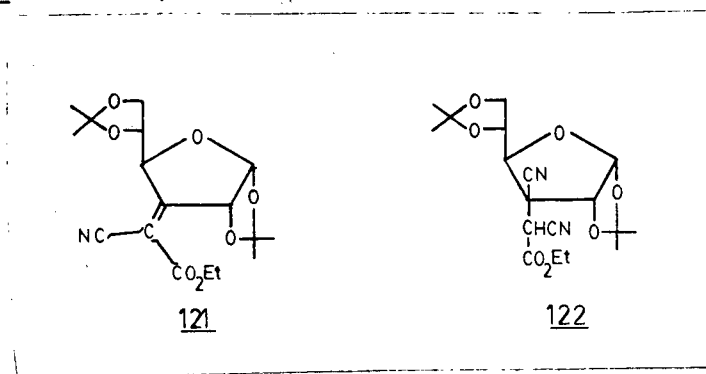
Zinner and co-workers¹⁹⁰ were able to condense ethyl cyanoacetate with 2,3:4,5-di-O-isopropylidene-D-arabinose using diethylamine as catalyst. The product was the unsaturated acyclic heptose 120. Stereochemical aspects of the reaction were



not discussed.

Concurrently with the present work, a report has appeared describing the condensation of the 3-ketose 14 with ethyl cyanoacetate under phase-transfer catalytic conditions to give

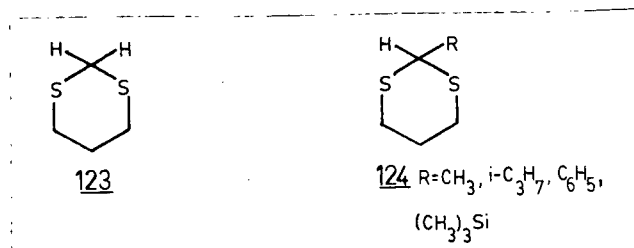
the branched-chain sugar 121. A Michael-addition of cyanide to the double bond of 112 then yielded the gem-di-C-alkyl derivative 122.¹⁹¹



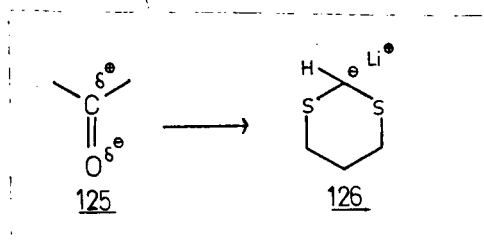
3. 1,3-Dithianes.

Two of the most desirable goals in synthetic organic chemistry are the formation of carbon-carbon bonds and the introduction into molecules of versatile functional groups amenable to further derivatization and modification. The anions of 1,3-dithiane¹⁹² (123) and 2-substituted 1,3-dithianes¹⁹²⁻¹⁹⁵ (124) have shown themselves in the past decade to fulfill both of these objectives at once by virtue of their highly nucleophilic properties and their ability to be converted under mild conditions to the synthetically useful carbonyl group. The dithiane system is also thermally stable as well as being relatively inert to acids and bases, making it even more valuable as a synthetic tool. Moreover, these thioacetals lack the overwhelming malodorousness generally associated with organic mercaptans.

1,3-Dithiane (123), first prepared and used synthetically by Corey and Seebach¹⁹² in 1965, is an example of a masked carbonyl which allows for a reversal, or umpolung¹⁹⁶, of the normal reactivity of this latter group. That is, whereas the



normal carbonyl (125) effectively carries a positive charge on the carbon atom to which nucleophiles can add,¹⁹⁶ the masked carbonyl, in the form of its thioacetal 126, is capable of supporting a negative charge on this same carbon so that it can now act as a nucleophile. Streitweiser¹⁹⁷ and Bernardi¹⁹⁸ have



independently concluded that the polarizability of sulfur rather than the availability of empty d-orbitals is responsible for the acidity of the α -hydrogens of the 1,3-dithiane system.

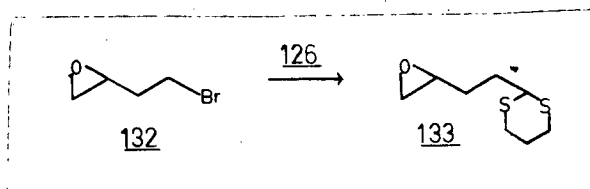
For brevity, the following discussion will restrict itself to the chemical properties of anions of the unsubstituted 1,3-dithiane system 123 unless otherwise noted. The chemistry of both 123 and 124 has been reviewed.^{194 199}

3.1 Nucleophilic Reactions of the 1,3-Dithiane Anion.

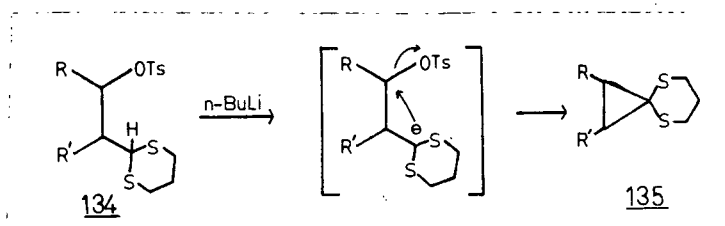
2-Lithio-1,3-dithiane (126), conveniently prepared¹⁹² by reaction of 1,3-dithiane with n-butyllithium at temperatures between -10° and -30° , reacts nucleophilically¹⁹⁹ with alkyl halides and benzenesulfonates, with epoxides, aldehydes, ketones, nitriles, amides, esters, and immonium salts. These reactions and their products are summarized in Table I.

The dithiane anion reacts with halides more readily than

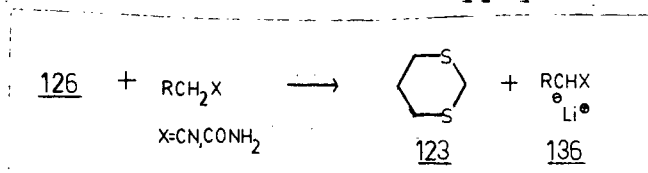
with epoxides, as shown by the exclusive formation of the epoxide 133 when the bromo epoxide 132 is treated with one equivalent of anion 126.²⁰⁰ Though epoxides are generally opened by dithiane to give the β -hydroxyalkylated derivative 128 (Table



I),²⁰¹⁻²⁰² cycloalkylation²⁰³⁻²⁰⁴ can be achieved by subsequently forming the p-toluenesulfonyloxy derivative 134. Addition of one equivalent of n-butyllithium then leads to intramolecular cyclization, yielding the cyclopropyl compound (135). Seebach and Wilka²⁰⁵ have observed that while such intramolecular displacements of tosylates proceed smoothly, benzenesulfonates are greatly superior for the analogous bimolecular reaction by which compounds of type 127 are generated.

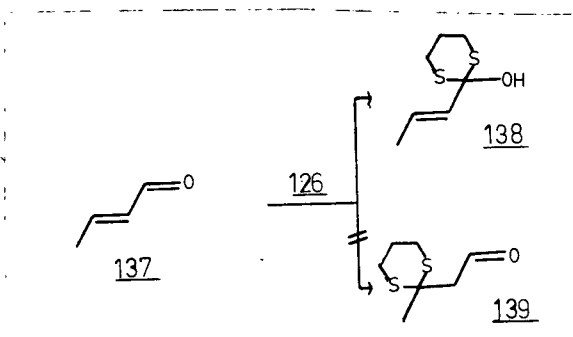


Acylation of 1,3-dithiane using amides or nitriles is practical only if the latter two groups have no α -hydrogens.²⁰⁶ In both cases, the α -hydrogens are more acidic than those of 1,3-dithiane so that metal exchange rather than addition occurs, producing 136. The same restrictions apply to reactions of the

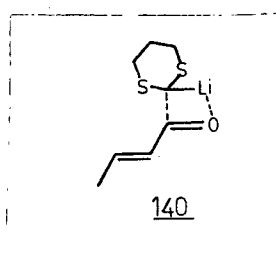


immonium salts.²⁰⁷⁻²⁰⁸

The addition of 2-lithio-1,3-dithiane to α,β -unsaturated carbonyls (137) generally occurs in a 1,2-fashion rather than in the conjugate Michael-type 1,4-fashion.¹⁹⁴ A transition state (140) in which the carbanion center cannot reach the γ -carbon

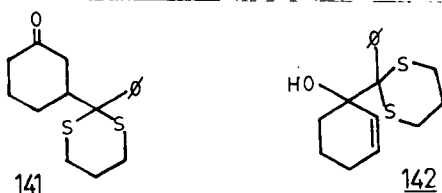


atom of the unsaturated system has been postulated in order to explain this phenomenon.²⁰⁹ However, this cannot account for the



fact that 2-substituted dithiane anions (124, $R=\text{COOCH}_3$,¹⁹⁹ SCH_3 ²¹⁰) often add exclusively in the 1,4-manner.

It has also been suggested that an equilibrium exists between the 1,2 and 1,4 addition products (138 and 139, respectively).²¹¹ This was demonstrated²¹² by the reaction of 2-lithio-2-phenyl-1,3-dithiane (124, $R=\text{C}_6\text{H}_5$) with 2-cyclohexanone; quenching of the reaction mixture at room temperature gave exclusively the 1,4-adduct 141 while quenching at -78° gave 65% of the 1,2-addition product 142. It was thus concluded that 1,4-addition is a thermodynamically-controlled process while 1,2-addition is kinetically favoured. In the case of addition of unsubstituted 1,3-dithiane, the equilibrium would lie far on the



side of the 1,2-adduct.

TABLE I: REACTIONS OF 2-LITHIO-1,3-DITHIANE (126)

Type of Reaction	Electrophile	Product	
Substitution	$R-X$ ($X=Cl, Br, I$)		127
	 ($R'=H, CH_3$)		127
Displacement			128
Addition	$R-C(=O)-R'$ ($R'=H, \text{alkyl, aryl}$)		129
Addition— Elimination	RCN		130
	$R_2C=NR_2^+$		131
	$RC(=O)NH_2$		130
	$RC(=O)OR'$		130

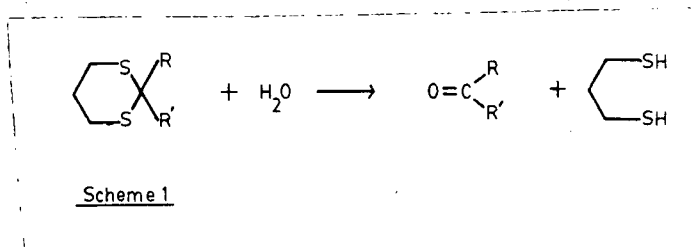
3.2 Conversion of 1,3-Dithianes to Carbonyls.

The need to have general, efficient methods of hydrolyzing the 1,3-dithiane group to a carbonyl group under mild conditions has produced several different approaches to this problem. The transition metal-induced hydrolysis of dithiane is an adaptation of Fischer's²¹³ use of mercuric chloride to hydrolyze his sugar ethyl S,S-acetals while the newer methods of oxidative and alkylative hydrolyses of thioacetals represent attempts to make the sulfur moiety a better leaving group. These will be

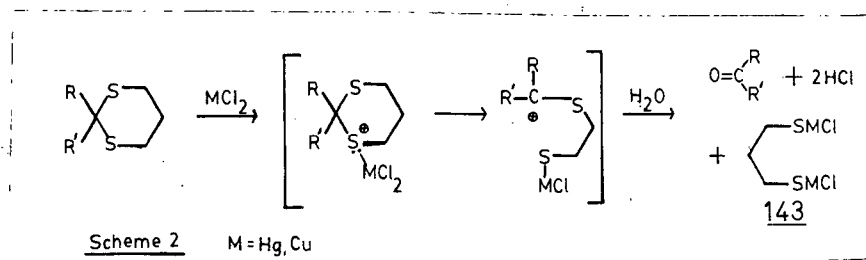
discussed in turn while other methods, such as direct hydrolysis with acid,²¹⁴ will be omitted since they cannot be considered as mild procedures.

3.2.1 Transition Metal-Induced Hydrolysis.

The hydrolysis of thioacetals is a reversible reaction which can be driven to completion only by removal of one of the products as it is formed (Scheme 1).²¹⁵ This is accomplished by use of a transition metal chloride which irreversibly binds with the thiol to form a metallothiolate (143, Scheme 2). The most

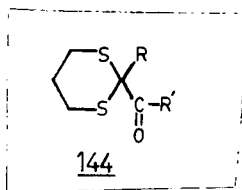


commonly used reagent of this type has been mercuric chloride,¹⁹⁴ though cupric chloride²¹⁶ has also been employed. The reaction is usually performed in aqueous polar organic solvents,²¹⁷ neutrality being maintained by the addition of insoluble carbonate salts²¹⁷⁻²¹⁸ or mercuric oxide²¹⁹ to remove the acid formed.

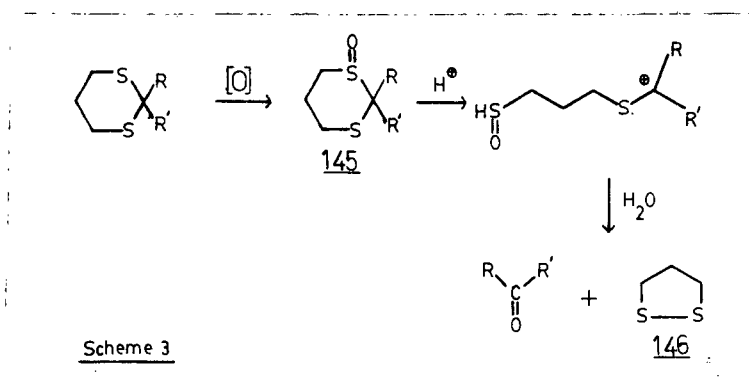


Though this method of hydrolysis appears to be general, it fails in the case of acyl 1,3-dithiane derivatives (144).^{217, 220}

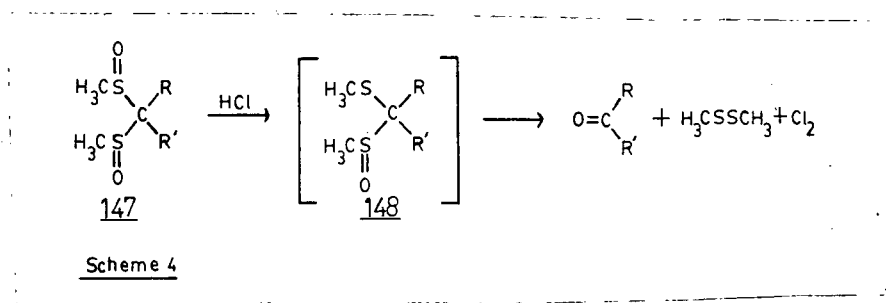
3.2.2. Oxidative Hydrolysis



Oxidation of a sulfur atom of a 1,3-dithianyl derivative to the S-oxide 145 permits mild acidic hydrolysis to the corresponding ketone or aldehyde (Scheme 3).²²¹⁻²²² Thiols are converted to the disulfide 146 in the process, ensuring complete reaction. The hydrolysis of disulfoxides (147, Scheme 4) to the



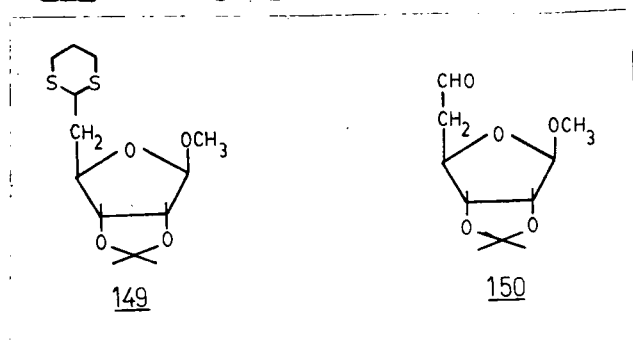
corresponding carbonyl derivatives with hydrogen chloride has also been shown to proceed via the monosulfoxides 148, some of which have been isolated.²²³



Among the reagents used to effect S,S-acetal hydrolysis via the S-oxide intermediate 145 are bromine²¹⁷, N-chloro-^{217 224} and N-bromosuccinimide.²¹⁷ The former is obviously incompatible with the presence of double bonds in the substrate to be hydrolyzed, a problem overcome by use of the N-halosuccinimides. The latter also promote hydrolysis of dithianes of type 144 to

the di-acyl derivatives.²¹⁷

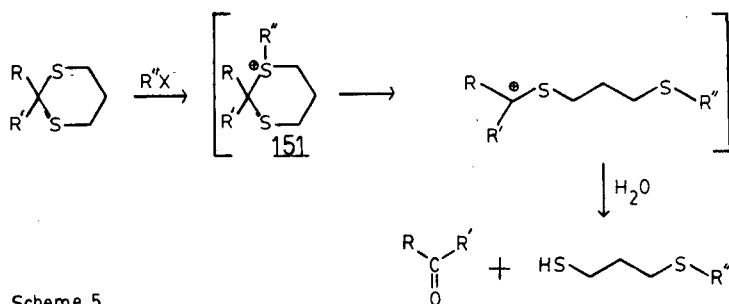
Ceric ammonium nitrate in aqueous acetonitrile converted the 5-C-dithianylribofuranoside 149 to the corresponding 5-C-formyl derivative 150 in high yield.²²⁵



Hydrolysis of the thioacetal of acetone has been accomplished using sulfuryl chloride and wet silica gel.²²⁶ Benzoyl peroxide was developed as an oxidative hydrolytic reagent for the dithiane moiety of squalenes when problems were encountered with the traditional mercuric chloride procedure.²²⁷

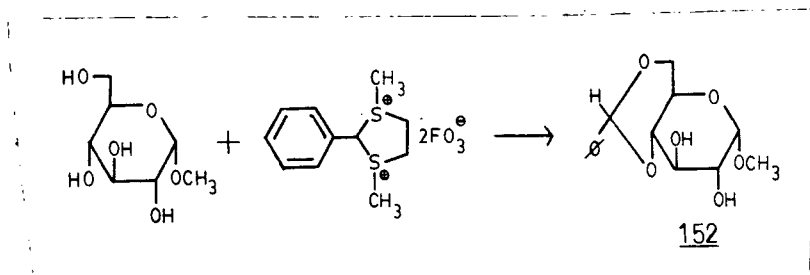
3.2.3. Alkylative Hydrolysis.

Alkylative hydrolysis of 1,3-dithiane derivatives proceeds via the sulfonium salts 151 (Scheme 5). Both the mono- and bis-sulfonium intermediates have been isolated.²²⁸⁻²³⁰



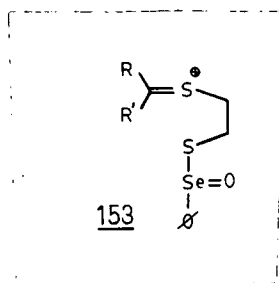
Alkylating agents employed have included methyl iodide²³¹ in aqueous acetone, acetonitrile or dimethylformamide,

trimethyl- or triethyloxonium tetrafluoroborate²²⁸⁻²³⁰ as well as methyl fluorosulfonate.²³² The latter reagent can also be used to promote conversion of thioacetals to acetals,²³³ a reaction which has found value in the formation of benzylidene derivatives of carbohydrates²³⁴ (152) under neutral conditions.



3.2.4. Miscellaneous Methods of Hydrolysis.

Barton and co-workers²³⁵ used benzeneseleninic anhydride to achieve hydrolysis of 1,3-dithiolan derivatives which were inert to other standard reagents. A selenenic intermediate of type 153 was postulated.



Mercuric oxide - boron trifluoride²⁰¹ has been developed as a hydrolytic system for the dithiane groups of sensitive molecules and has been used by Paulsen in the carbohydrate field.²³⁶

Dethioacetalization has also been accomplished photolytically.²³⁷

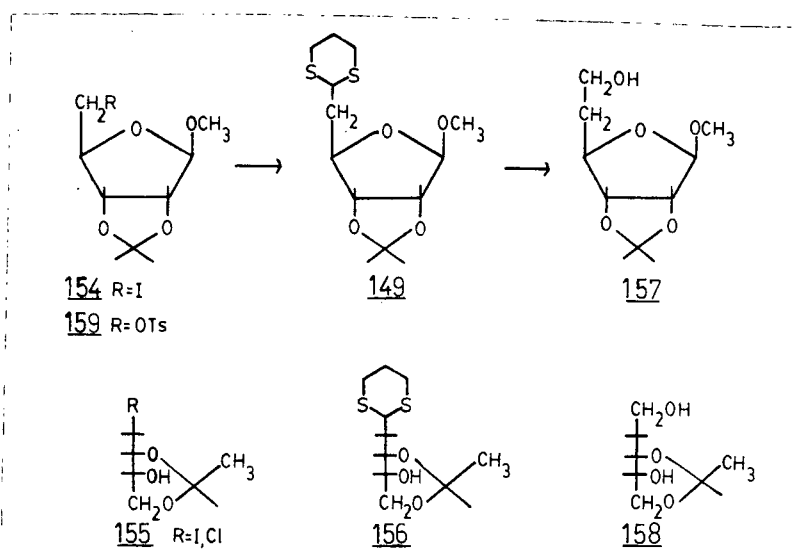
3.3 Reactions of 2-Lithio-1,3-dithianes with Carbohydrates.

The nucleophilic properties of anions of 1,3-dithianes (123 and 124) have been advantageously utilized in the synthesis of chain-elongated and branched-chain (A- and B- type) carbohydrates from suitably functionalized precursors. Such syntheses have been reviewed by Seebach,¹⁹⁹ Géro,¹¹ and Wander and Horton²³⁸ so that the following discussion will be restricted to the salient features of these procedures. There have been no reports of reactions between thioacetal anions and nucleoside derivatives.

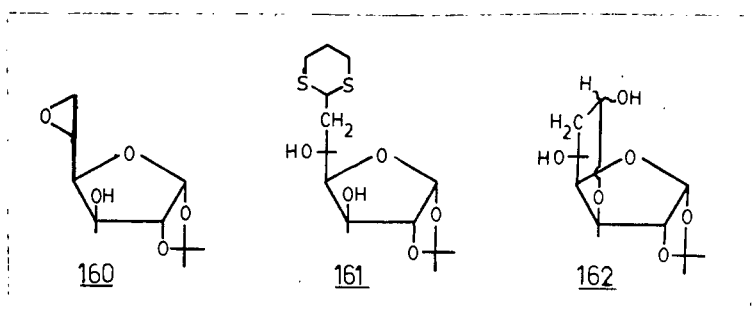
3.3.1. Chain-elongations of Carbohydrates.

Géro and co-workers²²⁵ were able to displace the primary halogens of the methyl ribofuranoside 154 and the acyclic erythritol 155 with 2-lithio-1,3-dithiane in hexamethylphosphoramide to afford reasonable yields of the dithianyl derivatives 149 and 156, respectively. Subsequent hydrolysis of the dithiane moieties of the latter two compounds with ceric ammonium nitrate (see Section 3.2.2.) followed by sodium borohydride reduction of the resulting formyl functionalities gave, respectively, the one-carbon chain-extended deoxy sugars 157 and 158. An attempted displacement of the primary tosylate of 159 gave only a 5% yield of 149, a not surprising result in view of later observations by Seebach and Wilka²⁰⁵ (see Section 3.1).

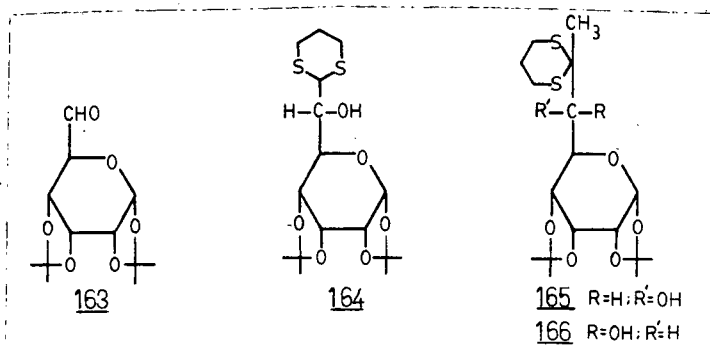
Chain-elongated deoxy-sugars were produced by displacement of the 5,6-epoxide of the partially unblocked furanose 160 with dithiane anion.²³⁹ Attack occurred exclusively at the primary position to give the adduct 161. Hydrolysis of the dithiane



group using boron trifluoride-etherate yielded the unusual tricyclic monosaccharide derivative 162.

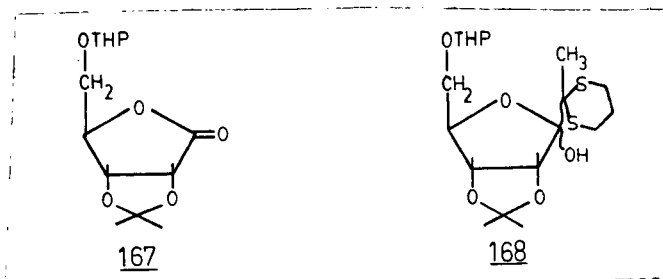


One- and two-carbon extensions could also be obtained from the dithianyl compounds formed by reaction of the exocyclic formyl group of 163 with the anion of 2-lithio-1,3-dithiane²⁴⁰ or 2-lithio-2-methyl-1,3-dithiane.²⁴¹⁻²⁴² Thus, while the L-glycero-D-galacto isomer 164 was produced exclusively when the reaction was run in tetrahydrofuran with 123²⁴⁰, 2-methyl-1,3-dithiane produced in the same solvent both possible C-6 epimers 165 and 166 in yields of 42% and 17% respectively.²⁴² Only the L-glycero derivative 166 was formed when the reaction was conducted in hexamethylphosphorictriamide.²⁴¹ Configurations



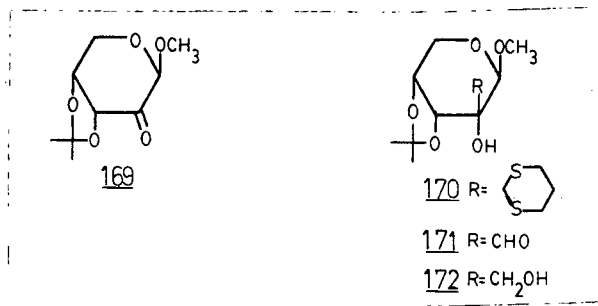
were determined by circular dichroism and by chemical correlations.

A precursor to C-nucleosides (see Section 4) (168) was formed when 2-lithio-2-methyl-1,3-dithiane was added to the lactone sugar 167.²⁴¹

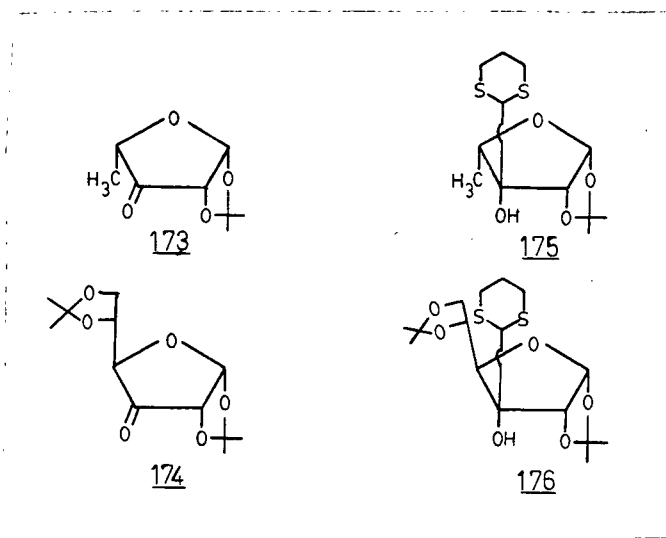


3.3.2. Synthesis of Type A Sugars.

Paulsen and co-workers,²³⁶ concurrently with Géro's group,²⁴⁰ prepared methyl D-hamameloside (172) by first adding 2-lithio-1,3-dithiane nucleophilically to the 2-ketoglycoside 169 and hydrolyzing the resulting product (170) to afford the formyl derivative 171 which was then reduced with sodium borohydride. The dithiane addition was stereoselective.



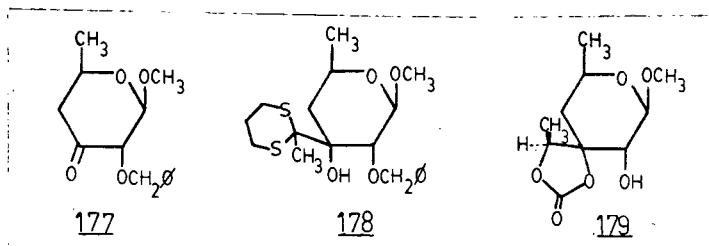
A similar stereoselectivity was observed in the addition of dithiane anion to the 3-ketoses 173 and 174 to give 175 and 176, respectively.²³⁶ In both cases, the anion attacks from the least sterically hindered side of the sugar molecule. Compound 175 has



served as a precursor in the synthesis of L-streptose (3)²³⁶ and its α - and β -glycosides²⁴³, analogues of streptomycin.

By reacting 2-lithio-2-methyl-1,3-dithiane with the 3-keto hexofuranose 177, the dithianyl adduct 178 was obtained which, by the sequence of oxidation, reduction, carbonate formation and debenzoylation, gave methyl β -D-alldgaroside (179).²⁴⁴⁻²⁴⁵ The configuration of the branched-chain of 179 was determined by comparison of its proton n.m.r. spectrum with those of the three other isomers obtained in the same reaction and from this information the complete structure of alldgarose, a sugar component of the antibiotic Alldgamycin E⁷, was proven.

Determination of the configuration at the branching point of such sugars as 170, 175, 176, and 178 was hampered by the fact that, there being no hydrogen atoms at these quaternary centers, no measurements of vicinal proton-proton spin-coupling values could be determined. Recourse was thus made to chemical

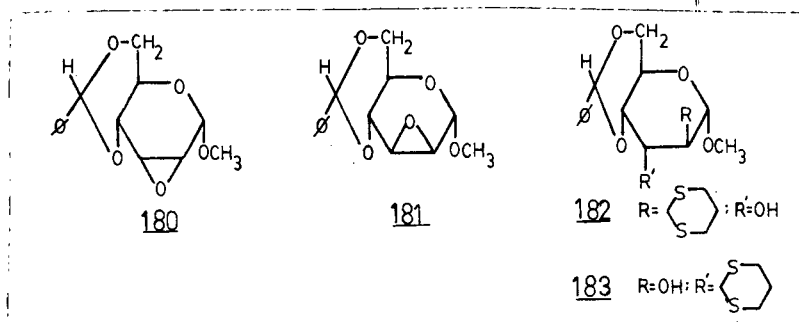


and optical correlations with known compounds.^{225 240-241 245} However, the use of single-crystal x-ray crystallography²⁴⁶ allowed unambiguous assignment of configuration of the L-streptose derivative 175. Géro and co-workers^{239 247-248} have employed comparison of ¹³C-n.m.r. values of closely related Type A branched-chain dithiane sugars to determine their stereochemistry. Also, configurational assignments have been made using lanthanide shift reagents and ¹H-n.m.r.²⁴⁹⁻²⁵⁰

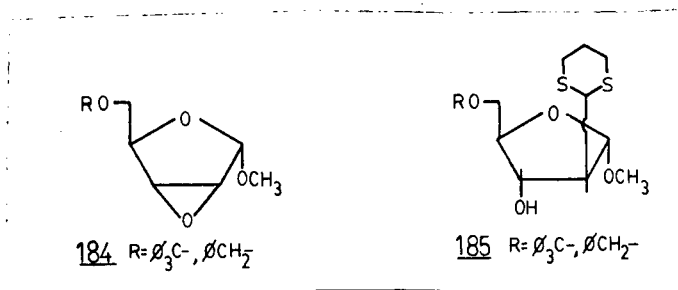
3.3.3. Synthesis of Type B Sugars.

The synthesis of Type B branched-chain sugars using 1,3-dithiane anions has proceeded mainly from displacement reactions with sugar epoxides. The dithiane nucleophile generally attacks in a regioselective manner, as was shown²³⁹ in the case of the terminal epoxide 160 (Section 3.3.1.).

Diaxial opening of the epoxide ring of both the D-allo- and D-mannopyranosides (180 and 181) by 2-lithio-1,3-dithiane was observed, giving, respectively, 3-C-dithianyl- and 2-C-dithianyl-altropyranosides (182 and 183).^{247 251}



Similarly, Yamashita and Rosowsky,²⁵² in their studies on the synthesis of arabinofuranosyl branched-chain sugars, discovered that 1,3-dithiane attacked preferentially at C-2 of the 2,3-anhydro sugar 184, presumably owing to steric interference by the bulky C-5 blocking group to C-3 attack, to give compound 185.



4. C-Nucleosides.

Compounds in which a heterocycle is attached to the anomeric carbon atom of a monosaccharide, usually ribose, by a C-C bond are referred to as C-nucleosides. The first example of a C-nucleoside, pseudouridine [5-(β -D-ribofuranosyl)uracil] (186), was isolated from an alkaline hydrolysate of calf liver RNA in 1959 by Cohn²⁵³, who also identified it.²⁵⁴⁻²⁵⁵ Since then, a number of other C-nucleosides have been isolated (see Figure I) from fermentation sources. All, except pseudouridine (186) possess antibiotic properties and some (e.g. oxazinomycin 187, showdomycin 188, formycin 189, and pyrazomycin 192) display antitumour and antiviral activities.^{19 256} The biological activities of C-nucleosides stem from the enhanced hydrolytic stability of the glycosidic carbon-carbon bond compared to the more labile carbon-nitrogen bond of the common nucleosides.²⁵⁷ Moreover, C-nucleosides, being structurally related to the normal N-nucleosides can replace these latter compounds in the

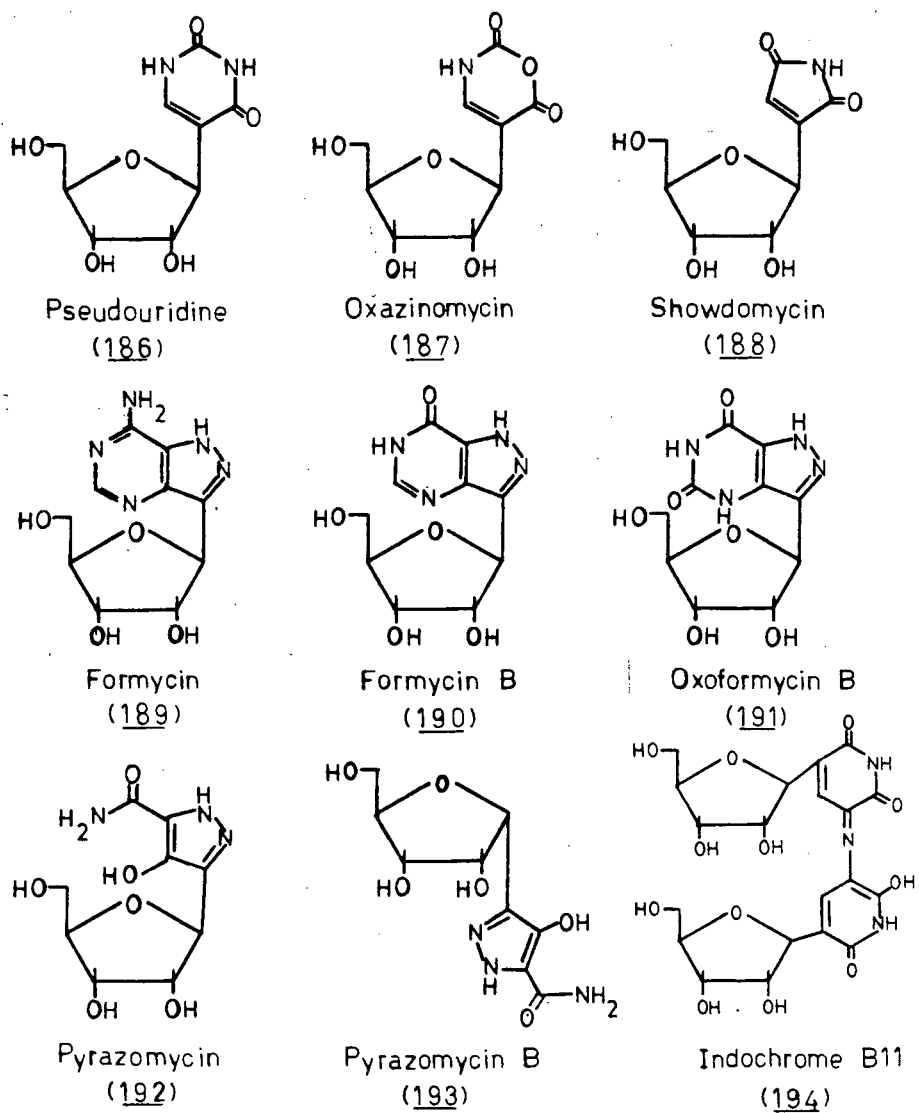


Figure I: Naturally - Occurring C-Nucleosides

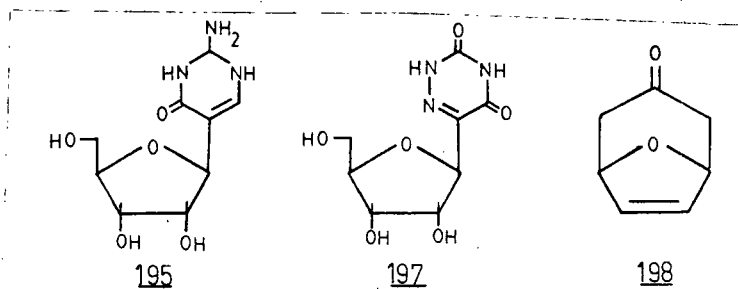
enzymic reactions associated with metabolism and tRNA synthesis and consequently interfere with these processes.²⁵⁸

Because the biological properties^{19 256} of C-nucleosides, as well as the synthesis²⁵⁹⁻²⁶⁰ of both natural C-nucleosides and their analogues, have been exhaustively reviewed, a detailed account of such topics in these pages would be redundant. The following, then, is a brief discussion of the general approaches to C-nucleoside synthesis that are relevant to the present work.

4.1 Synthesis of C-Nucleosides and Their Analogues.

A great number of analogues^{256 260} of the naturally-occurring C-nucleosides have been synthesized over the last decade in an effort to obtain more physiologically effective and specific compounds. The success in this endeavour has been highlighted by the synthesis²⁶¹ of pseudo-isocytidine [5-(β -D-ribofuranosyl)isocytosine] (195), the first synthetic C-nucleoside to display antitumour properties.²⁶²

Four synthetic strategies have been employed to produce novel C-nucleosides. The first involves modification of naturally-occurring C-nucleosides. For instance, Šorm and associates²⁶³ prepared 6-azapseudouridine (197) by ozonolysis of pseudouridine (186) followed by cyclization of the derived thiosemicarbazone. A second approach to C-nucleoside synthesis involves the use of non-carbohydrate precursors. Thus, by a series of reactions, Sato and co-workers²⁶⁴ were able to elaborate the oxabicyclooctenone 198 in a stereocontrolled manner to give a variety of pseudouridine derivatives including pseudo-isocytidine (195).

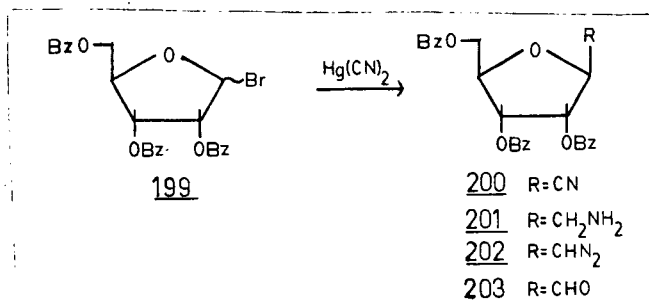


The direct coupling of a preformed heterocycle with an appropriately blocked sugar derivative represents the third and most direct way of synthesizing C-nucleosides. The intermediacy of metallated heterocyclic bases is generally required²⁶⁵ and this will be discussed more fully in the following section (see Section 5.1).

By far the most practical synthetic route to modified C-nucleosides consists of functionalization of a sugar derivative at C-1 followed by a stepwise elaboration of a heterocyclic base from this functional group. Two methods of obtaining such C-glycosides will be described, the first proceeding from glycosyl cyanides and the second from condensations of carbanions with glycosyl halides.

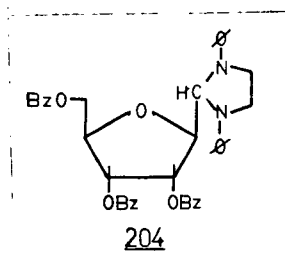
4.1.1. Glycosyl Cyanides.

Based on previous work by Coxon,²⁶⁶ Bobek and Farkaš²⁶⁷ prepared the tri-*O*-benzoylated ribofuranosyl cyanide 200 in high yield by reacting the bromide 199 with mercuric cyanide in nitromethane. Only the β -isomer was obtained, presumably owing to neighbouring-group participation. The orientation of the C-1 substituents of C-glycosides is critical in the synthesis of C-nucleosides since, but for a few exceptions²⁶⁸⁻²⁶⁹ only the β -derivatives of the latter compounds exhibit therapeutic activities. The nitrile group of 199 could be reduced with lithium aluminum hydride to the primary amine 201 which in turn



was converted to the diazo derivative 202.²⁷⁰ Compound 202 served as starting material for synthesis of formycin B²⁷¹ (190) and oxoformycin B²⁷⁰ (191).

Alternatively, the glycosyl nitrile could be reductively hydrolyzed to the corresponding aldehyde (203) with Raney nickel and sodium hypophosphite.²⁷² Because of troublesome β -elimination of benzoate groups during this reaction, the aldehyde 203 was trapped as the N,N'-diphenylimidazolidine derivative 204 as it was formed. The aldehyde 203 could be

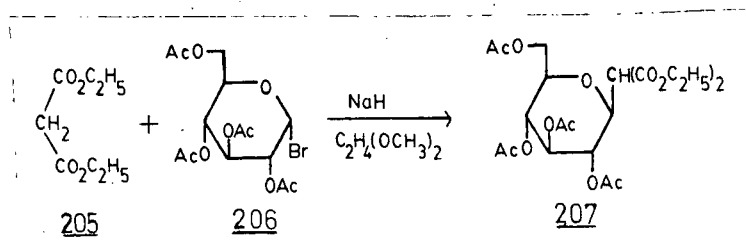


regenerated from 204 by mild acid hydrolysis. Compound 203 was a key intermediate in a simplified synthesis²⁷³ of showdomycin (188) and has been elaborated into a variety of C-nucleoside analogues.²⁶⁰

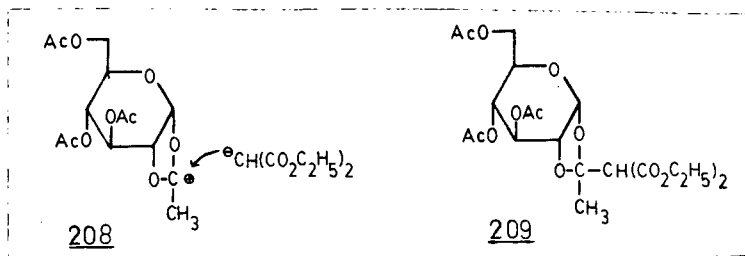
4.1.2 Condensations with Carbanions.

Hanessian and co-workers²⁷⁴⁻²⁷⁵ have reported the reaction of diethyl sodiomalonate (205) with different glycosyl halides. In their initial study, reaction of 205 with the acetylated glucopyranosyl bromide 206 in 1,2-dimethoxyethane gave the C-

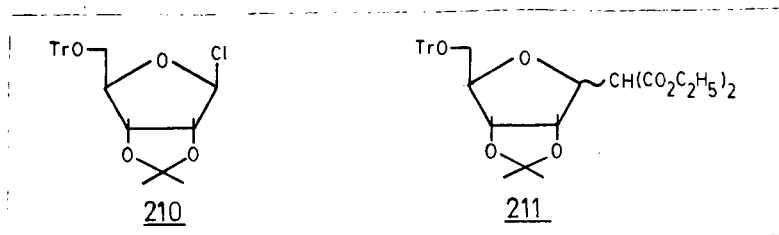
glycosyl malonate 207. Only the β -isomer of 207 was produced.



When a polar solvent such as N,N-dimethylformamide was used as the reaction medium, an appreciable quantity of compound 209 was isolated, this product arising from attack of the carbanion at the dioxolenium carbon atom of the intermediate acetoxonium ion 208. Subsequent investigations were thus concerned with the use of non-participating blocking groups in the reacting sugar halide in order to avoid this competing side reaction.



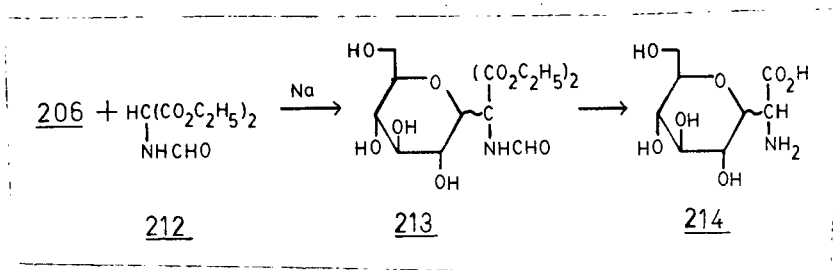
Ohrui and Fox²⁷⁶ used the β -chloro ribofuranoside 210 in an extension of Hanessian's original work, obtaining an α,β -mixture of the malonates (211). Equilibration of this mixture in ethanol-sodium ethoxide yielded exclusively the α -isomer of 211.²⁷⁷



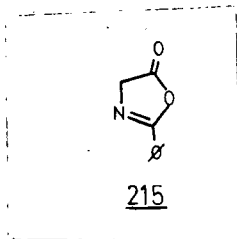
Triethyl sodioethanetricarboxylate²⁶⁰ and ethyl acetoacetate²⁷⁶ have also been reacted with ribofuranosyl

halides to give the corresponding C-glycosides.

The attachment of α -amino acids at the anomeric carbon of sugars by a C-C bond has lately been of interest because such derivatives are highly functionalized and can thus be conveniently elaborated to C-nucleosides. These compounds also allow easy access to those C-nucleosides in which C-1 of the aglycon is attached to a carbon and a nitrogen (for instance, compounds 189-193). The first synthesis of such amino acid C-glycosides proceeded from the reaction of the sodium salt of diethyl 2-formamidomalonate (212) with the bromo sugar 206 in ethanol to give the C-glycoside 213 which was then converted to the glycine derivative 214.²⁷⁸ Later attempts to repeat the work failed.²⁷⁴

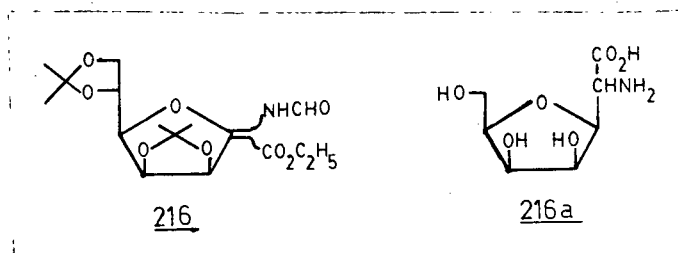


Rosenthal and Brink²⁷⁹ obtained compound 214 by reacting 206 with the anion of 2-phenyloxazol-5-one (215) followed by base hydrolysis of the product.



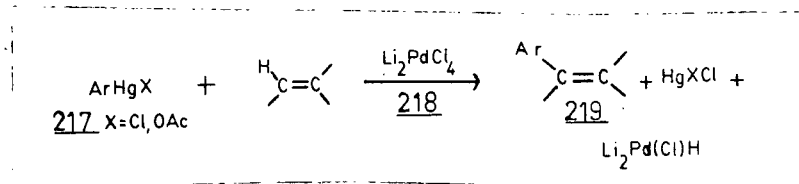
The synthesis of C-glycosyl glycines was extended to a furanosyl sugar by Hall and co-workers²⁸⁰ by reacting the potassium salt of ethyl isocyanoacetate with a blocked D-mannono-1,4-lactone to give 216. Catalytic hydrogenation of 216 followed by hydrolysis yielded the lyxofuranosyl D- and L-

glycines 216a.

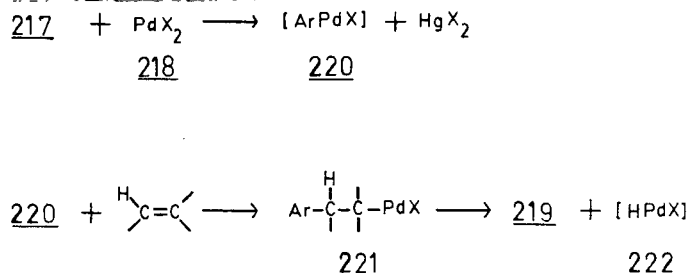


5. Palladium-Catalyzed Synthesis of Modified Nucleosides.

The use of organopalladium intermediates for the formation of carbon-carbon bonds is well known and has been reviewed.^{280a} Heck,²⁸¹ using arylmercuric salts (217) and lithium palladium chloride (218) was able to arylate olefins in varying yields. A

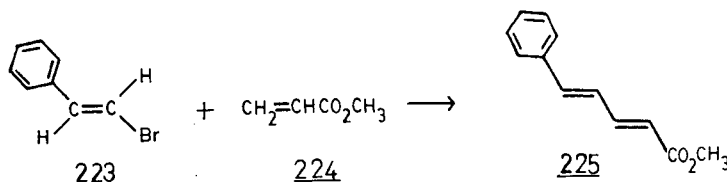


mechanism was postulated (Scheme 6) in which the initially formed arylpalladium intermediate 220 added to the olefinic double bond to give the sigma complex 221. Spontaneous decomposition of 221 then yielded the olefin (219) and the metal hydride 222. The latter compound could then be converted to the catalytically active form (218) by including an oxidizing agent such as cupric chloride in the reaction mixture. This general arylation reaction was extended to allylic alcohols,²⁸²⁻²⁸³, allylic halides²⁸⁴, enol esters²⁸⁵, enol ethers²⁸⁵, and carbon monoxide.²⁸⁶

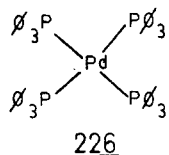


Scheme 6

The arylation reaction could be performed with aryl halides instead of arylmercuric salts (217) if palladium metal was used as the catalyst,²⁸⁷ the active species 220 being formed by oxidative addition of the metal to the halide. Moreover, it was shown²⁸⁸ that the vinyl hydrogen atom of methyl acrylate (224) could be displaced by trans- β -bromostyrene (223) under these conditions to give the diene 225 in moderate yields. Better yields and more stereoselectivity were achieved in these

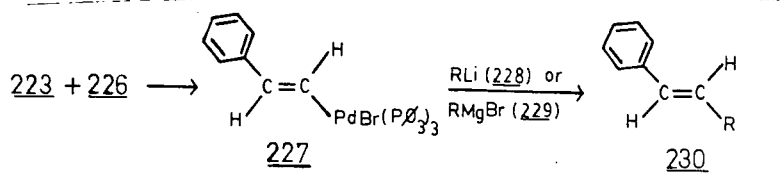


reactions when triphenylphosphine was used in conjunction with the palladium metal to form tetrakis(triphenylphosphine)palladium (0) (226).²⁸⁹



The phosphine complex 226 also catalyzes the coupling of vinyl halides (e.g. 223) and alkyllithium compounds²⁹¹ (228) or Grignard reagents²⁹⁰⁻²⁹¹ (229) to give, in both cases, exclusively the cis or trans product 230 in high yields via the organopalladium intermediate 227.

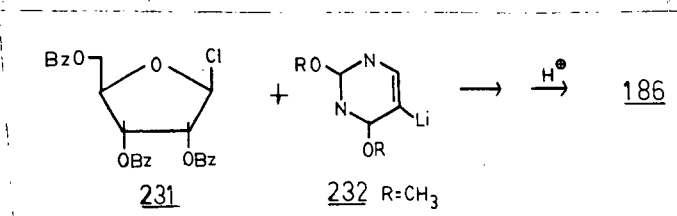
The general principles just described have been successfully employed in the synthesis of modified nucleosides.



This is discussed next.

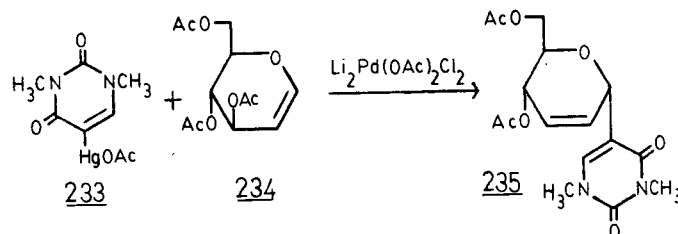
5.1 Synthesis of C-Nucleosides via Organopalladium Intermediates.

The direct synthesis of C-nucleosides (see Section 4) by coupling of a heterocyclic base with a suitable sugar derivative is not yet an entirely satisfactory operation. The first such attempt was reported by Shapiro and Chambers²⁹² who condensed the chloro sugar 231 with the 5-lithiouracil derivative 232. Pseudouridine (186) was obtained in only 2% yield after removal of the blocking groups.



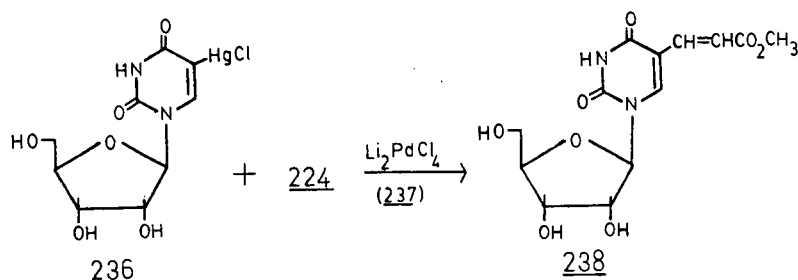
Slight improvements were made in the yields of pseudouridine (186) by reacting 5-lithiouracil derivatives (232, $\text{R} = \text{Me}_3\text{C}-$, CH_2) with a blocked aldopentose derivative²⁹³ and a ribonolactone derivative.²⁹⁴

Recently the direct, palladium-catalyzed coupling of the 5-mercuriacetyluracil derivative 233 with the triacetylated glucal 234 was reported²⁹⁵ to give the C-nucleoside analogue 235 in 20% yield. Spontaneous deacetylation and opening of the pyranose ring were the main disadvantages of the reaction sequence.



5.2 Synthesis of Pyrimidine Nucleosides Modified at C-5 using Organopalladium Intermediates.

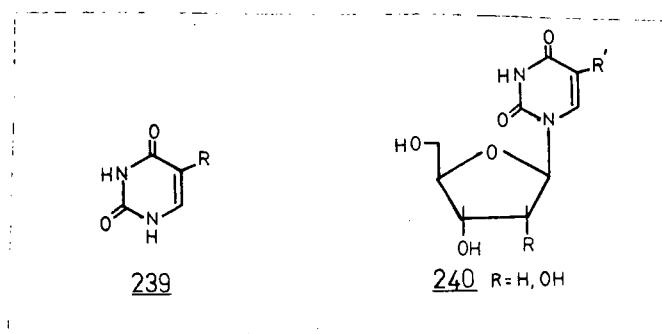
Bergstrom and coworkers²⁹⁶⁻²⁹⁷ have recently described the palladium-catalyzed alkylation of the C-5 position of uridine and 2'-deoxyuridine. For example, reaction of 5-chloromercuriuridine (**236**) with methyl acrylate (**224**) in the presence of the palladium catalyst **237** gave the trans derivative **238**.



Pyrimidine nucleosides substituted at C-5 display in many cases chemotherapeutic properties.²⁹⁸⁻³⁰¹

6. Modified Pyrimidine Bases and Their Nucleosides

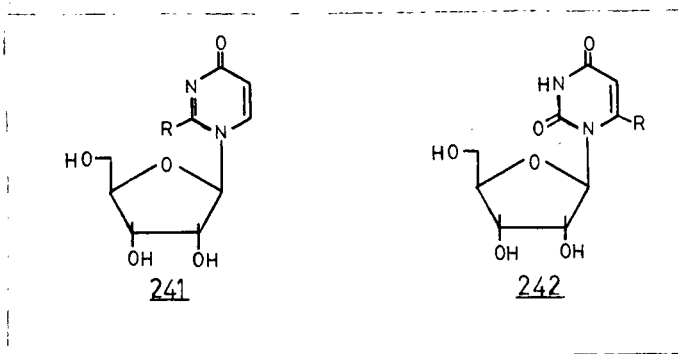
Uracil derivatives modified at C-5 (239) represent an interesting class of compounds displaying antiviral, anticancer or mutagenic properties.³⁰² For example, 5-fluorouracil (239, R=F) is used clinically in the treatment of leukemia. Because the physiological activity of 5-fluorouracil has been linked with the stability of the carbon-fluorine bond³⁰³, the incorporation of such stable linkages in the form of carbon-carbon bonds (239, R=alkyl, aryl etc.) has been pursued in the interests of producing medicinally valuable analogues. Thus, pseudouridine (186, Section 4) and its derivatives may be considered as C-5 modified uracil compounds (239, R=ribofuranosyl).



Though uracil derivatives of type 239 are potentially valuable in themselves they can also be converted by conventional techniques to C-5 substituted nucleosides (240), another class of clinically useful compounds (see Section 5.2).²⁹⁸⁻³⁰³ In this case, the nucleosides can display biological activities completely different from those of the parent base. For example, 5-fluorodeoxyuridine (240, R'=F, R=H) is an antiviral agent as well as an anticancer agent.³⁰⁰⁻³⁰¹

The biological studies of nucleosides substituted at C-2 (241) or C-6³⁰⁴ (242) have not received the attention accorded the C-5 analogues (240) mainly because problems encountered in

their syntheses have made very few of these compounds available. However, the finding that naturally-occurring orotidine (242, $R=COOH$) is essential for the biosynthesis of RNA pyrimidine nucleosides in mammalian systems³⁰⁵ is an indication that C-6 modification of this compound may have important physiological implications.

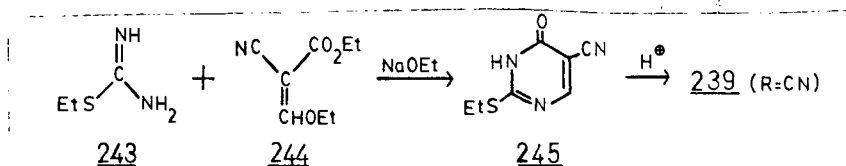


The following, then is a brief discussion of the more practical methods of introducing carbon-carbon linked substituents at C-5 of uracil derivatives (239) and C-2 and C-6 of pyrimidine nucleoside derivatives (241 and 242, respectively).

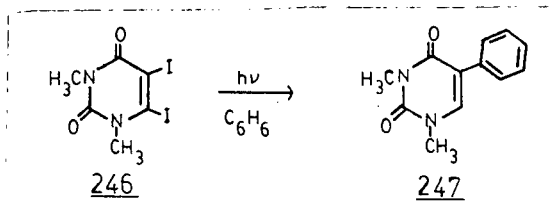
6.1 Introduction of C-C Linked Substituents at C-5 of Uracil Derivatives.

Pyrimidines substituted at C-5 (239) can be synthesized by condensation of appropriately functionalized components. Thus, reaction of ethylisothiourea (243) with ethyloxymethylenecyanoacetate (244) in the presence of base gives a 5-cyano derivative (245) which can be hydrolyzed to 5-cyanouracil (239, $R=CN$).³⁰⁶ This method is limited by the availability of the necessary three-carbon precursors.

Aromatic substituents can be photolytically attached to C-5 of uracil derivatives. Irradiation of a solution of 5,6-diiodo-



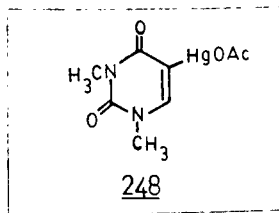
1,3-dimethyluracil (246) in benzene gave the 5-phenyl adduct 247 by a free-radical mechanism.³⁰⁷



The direct introduction of a functional group at C-5 that can be further modified to give any type of side-chain is perhaps the best approach to altering pyrimidines at this position. Toward this end, the highly versatile 5-formyluracil (239, R=CHO) has been synthesized in high yield by condensation of formaldehyde with uracil (239, R=H) under acid or base catalysis, followed by manganese dioxide oxidation of the resulting 5-hydroxymethyluracil (239, R=CH₂OH).³⁰⁸

The use of 5-lithiouracil derivatives (232) as precursors to C-5 ribosylated compounds has been discussed (see Section 5.1).

Finally, the synthesis of a stable C-5 mercurated uracil derivative (248)³⁰⁷ has opened the way to modification of this position using the palladium-catalyzed reactions discussed previously (see Section 5).

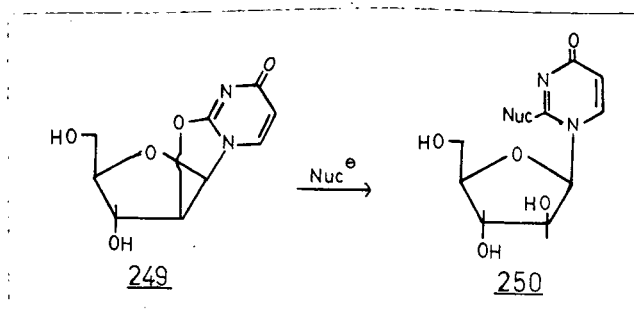


6.2 Synthesis of Base-Modified Pyrimidine Nucleosides.

6.2.1. Modifications at C-2.

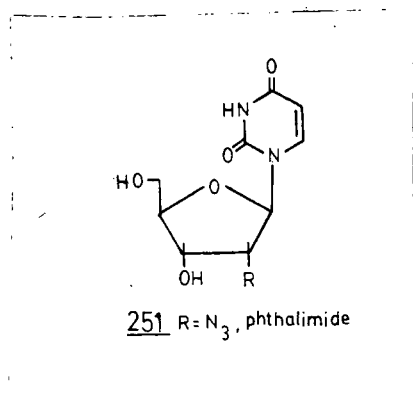
The synthesis of modified nucleosides of type 241 by direct

condensation of a 2-substituted uracil derivative and a sugar would appear to be sterically unfavourable by analogy with the synthesis of 6-substituted nucleosides of type 242 (see Section 6.2.2.1.). The most convenient route to C-2 modified nucleosides involves the intermediacy of 2,2'-anhydronucleosides (249), the chemistry of which has been reviewed by Fox.³⁰⁹ Various nucleophiles are known to attack the anhydro linkage of 249 at



C-2 to give the 2-substituted arabino nucleosides of type 250. Thus, reaction of 249 with hydroxide, methoxide, ammonia or hydrogen sulfide³¹⁰ gives 250 in which R is respectively OH, CH₃O, NH₂ or HS. Introduction of a C-C linked substituent at C-2 has been achieved³¹¹ by reaction of an anhydronucleoside with dimethyloxosulfonium methylide to give 250 (R=Me₂ $\overset{\overset{\text{O}}{\parallel}}{\underset{\underset{\ominus}{\text{S}}}{\text{C}}}$ -CH). Pyrimidine nucleosides having the arabino configuration (e.g. 250) are medically valuable compounds.³⁰¹

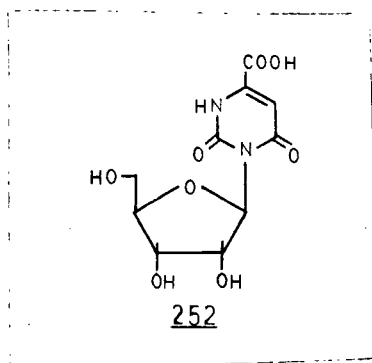
The main disadvantage of this method of synthesizing modified nucleosides lies in the inability to predict the position of attack of a particular type of anion; both azide³¹² and phthalimide³¹³ anion attack on the sugar portion of the anhydro linkage of 249 to give C-2' modified nucleosides (251).



6.2.2. Modifications at C-6.

6.2.2.1. Direct Condensation.

The first synthesis of orotic acid (242, R=COOH) was achieved in only 8% yield by Curran and Angier³¹⁴, who condensed the mercury salt of n-butyl orotate with tribenzoylribofuranosyl chloride. The main product (10%) was the sterically favoured N-3 glycoside 252. Other studies³¹⁵⁻³¹⁷ concerned with the direct coupling of 6-methyluracil derivatives with sugar halides showed



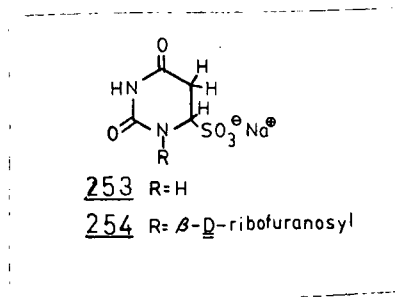
that the N-3 glycoside was again the favoured product, though

conditions could be altered to render acceptable yields of the N-1 glycoside (242, R=CH₃).

Proceeding from such a modified condensation reaction, Klein and Fox³¹⁸ were able to oxidize the methyl group of 242 (R=CH₃) with selenium dioxide to give 6-formyluridine (242, R=CHO), an important intermediate for further derivatization of the C-6 position.

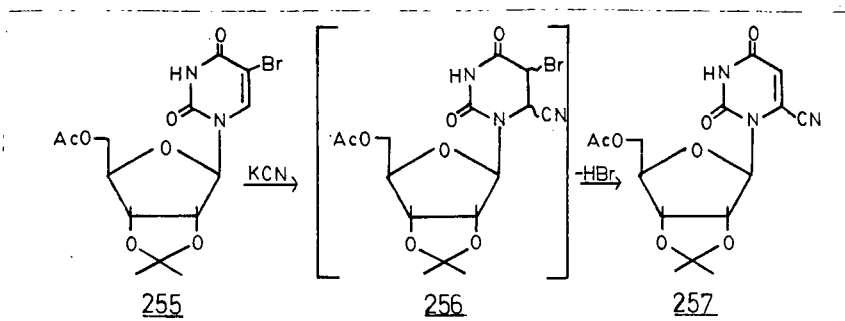
6.2.2.2. Nucleophilic Substitution.

The 5,6-double bond of uracil and its derivatives is known to be susceptible to nucleophilic attack.³⁰³ For instance, sodium bisulfite adds to uracil or uridine in a reversible manner to give the 6-bisulfite adducts 253 and 254, respectively.³¹⁹



By reacting potassium cyanide with the blocked 5-bromouridine derivative 255 in pyridine, Ueda³²⁰ obtained the 6-cyano adduct 257. The reaction was thought to proceed by initial nucleophilic addition of the cyanide anion to C-6 of the 5,6-double bond of 255 to give the intermediate 256. Spontaneous elimination of hydrogen bromide then gave 257. This addition-elimination mechanism was confirmed by deuteration studies of the analogous potassium cyanide- 5-bromouracil system³³⁰.

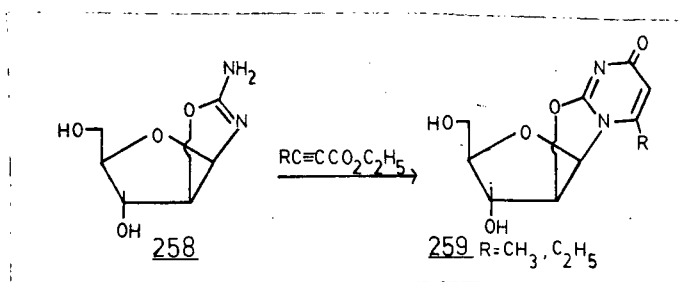
Ueda was further able to convert the C-6 nitrile group to a



variety of other functionalities by standard procedures.³³¹ This is the only example of nucleophilic introduction of a carbon unit at C-6 of uridine.

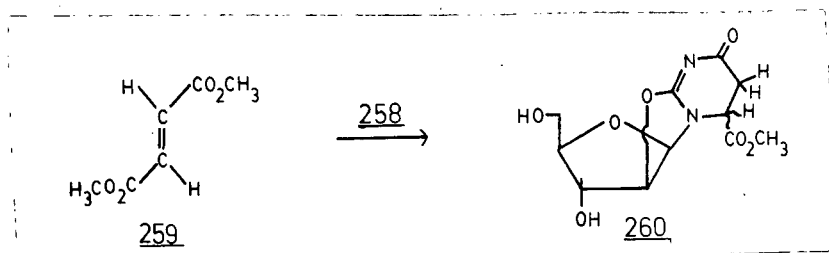
6.2.2.3. Synthesis from Oxazolines.

Holý³³² has successfully reacted, under base catalysis, the 2-amino oxazolino sugar **258** with alkyl 2-butynoates to give the C-6 alkylated 2,2'-anhydronucleoside **259**. These



anhydronucleosides are easily converted to the 6-alkyl ribo, arabino or 2-deoxy nucleosides.³³³

Similarly, Hall and co-workers³³⁴ were able to synthesize various novel 6-substituted 2,2'-anhydro-5,6-dihydro nucleosides by reacting **258** with activated α, β -unsaturated esters. Thus, **258** and dimethyl fumarate (**259**) gave the 6-carbomethoxy derivative **260**.



6.2.2.4 Miscellaneous Methods.

Alkyl groups have been attached to C-6 of uridine by photochemical means³³⁵⁻³³⁶ and by Claisen rearrangement of 5-allyloxyuridine.³³⁷

III RESULTS AND DISCUSSION

The work to be described has been divided into three basic units. These are: (1) The synthesis of glycosyl α - and β -amino acids that are structural analogues of the sugar moiety of the polyoxins, (2) the synthesis of C-nucleosides and their precursors, and (3) the attachment of C-C linked substituents at C-2 and C-6 of pyrimidine nucleosides. Each unit has been organized according to the following headings:

1. Glycos-3-yl Amino Acids: Structural Analogues of the Sugar Moiety of the Polyoxins.

1.1. Synthesis of Derivatives of Glycos-3-yl β -Alanine:

Application of the Knoevenagel Condensation of Ethyl Cyanoacetate with a 3-Ulose.

1.2. Synthesis of Derivatives of Glycos-3-yl Glycine:

Application of the Bucherer Procedure via Condensation of 1,3-Dithiane Anion with a 3-Ulose.

2. Synthetic Approaches to C-Nucleosides.

2.1. Synthesis of Functionalized Precursors to C-Nucleosides.

2.1.1. Knoevenagel Condensation of Ethyl Cyanoacetate with a 2,5-Anhydro-D-allose.

2.1.2. Condensation of Diethyl Sodium Phthalimidomalonate with a Glycosyl Halide.

2.2. Synthesis of 5-Alkyl Uracil. Attempted One-Step Synthesis of a Pseudouridine Derivative.

3. Modifications of the 2- and 6-Positions of Uridine Using 1,3-Dithiane Anion.

3.1. Reaction of 1,3-Dithiane Anion with a 2,2'-

Anhydronucleoside: Functionalization of the 2- and 6-Positions of Pyrimidine Nucleosides.

3.2. Reaction of 1,3-Dithiane Anion with Blocked 5-Bromouridine: Synthesis of a 6- β -Alanine Derivative of Uridine.

1. Glycos-3-yl Amino Acids: Structural Analogues of the Sugar Moiety of the Polyoxins.

The synthesis of branched-chain glycos-3-yl amino acids has been a subject of continuing interest in our laboratory.⁶⁸⁻⁷² The objective has been to form analogues of the sugar moiety of the naturally-occurring polyoxins (see Introduction, Section 1.3.), the nucleosides of which might exhibit interesting biological properties.¹⁸ Since previous synthetic studies have focussed on the attachment of α -amino acids, notably glycine and alanine,⁷⁷ to suitable carbohydrate derivatives by carbon-carbon bonds, it seemed natural to extend this work to the hitherto unknown β -amino acid sugar derivatives. Such compounds could be of value in elucidating structure-activity relationships of the various molecules synthesized.

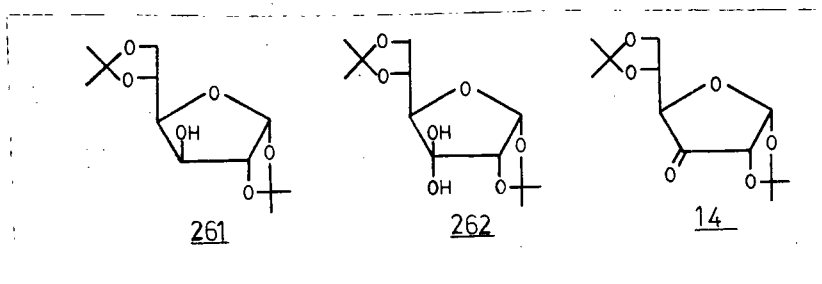
It was also our goal to find more efficient and convenient methods of synthesizing those glycos-3-yl α -amino acids which had already been produced by various means in our laboratory. Such new procedures, it was felt, should yield branched-chain derivatives whose nucleosides could easily be formed.

1.1. Synthesis of Derivatives of Glycos-3-yl β -Alanine: Application of the Knoevenagel Condensation of

Ethyl Cyanoacetate with a 3-Ulose.

1.1.1. 1,2:5,6-Di-O-isopropylidene- α -D-ribo-hexofuranos-3-ulose (14).

Oxidation of the free hydroxyl group of 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose (261)³³⁸ was achieved by known procedures using ruthenium tetroxide³³⁹⁻³⁴⁰, generated in situ. The resulting ketose hydrate (262) was dehydrated to 3-ulose 14 by azeotrope with toluene immediately prior to use.



1.1.2. Knoevenagel Condensation of Ethyl Cyanoacetate (263) with 1,2:5,6-Di-O-isopropylidene- α -D-ribo-hexofuranos-3-ulose (14).

The conditions used by Rosenthal and Cliff⁷² in their condensation of methyl nitroacetate with 14 were adapted for the present study. Thus, reaction of the 3-ulose 14 with a slight molar excess of ethyl cyanoacetate (263) in N,N-dimethylformamide using ammonium acetate as the catalyst gave, after 2 hours at room temperature, two major new products as shown by t.l.c. on silica gel. Though t.l.c. still showed presence of some unreacted starting material in the reaction mixture, increasing the reaction time resulted in the formation of a considerable number of side-products so that 2 hours was considered the optimum reaction time.

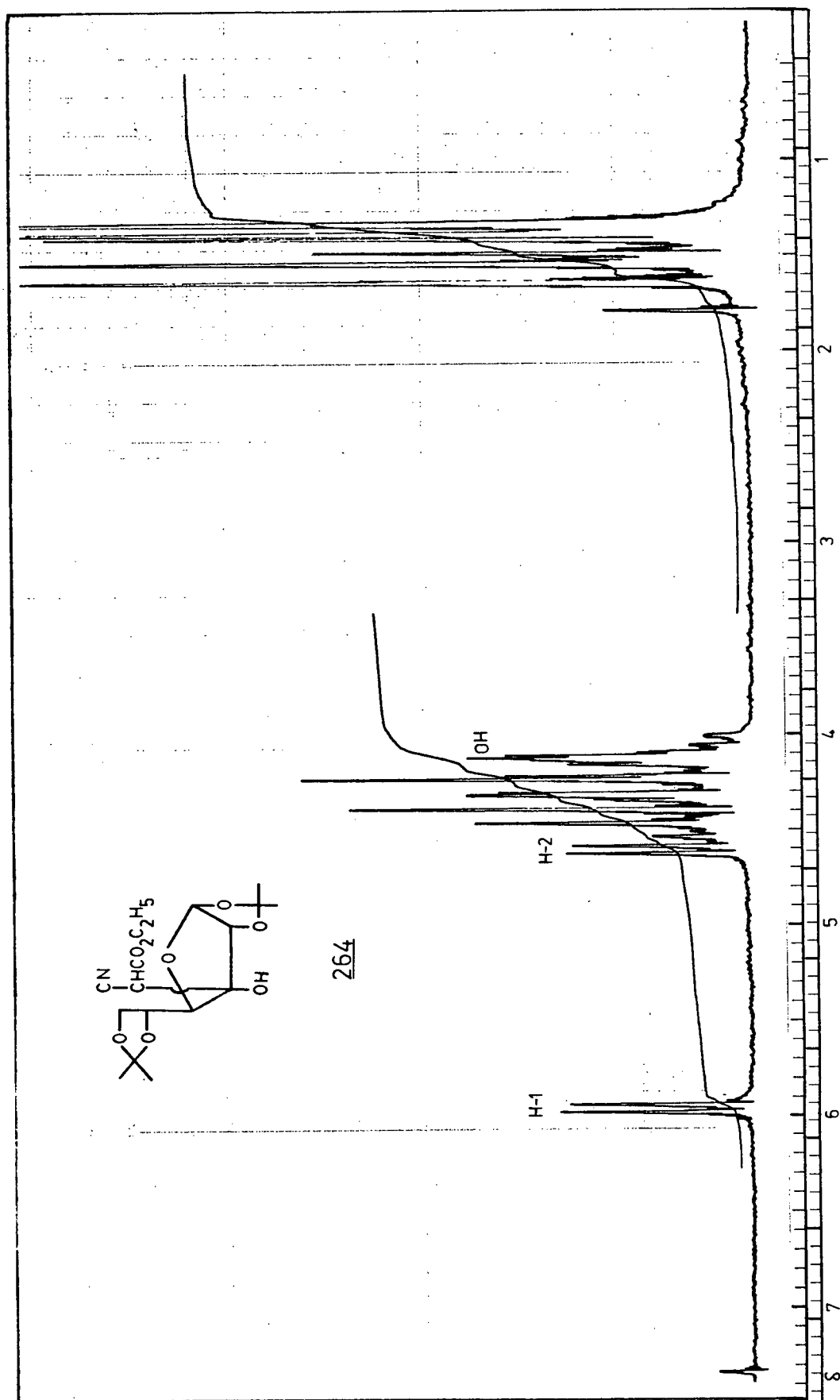
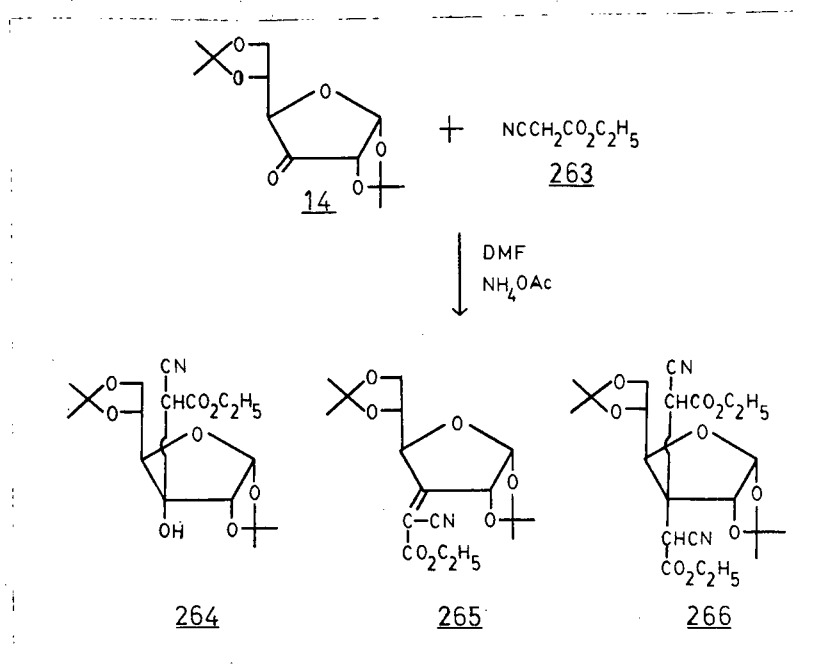


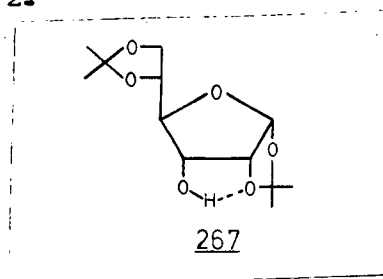
Figure II. Partial 100 MHz PMR Spectrum of 3-C-[(R,S)-Cyano(ethoxycarbonylmethylene)]-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (264) in CDCl₃.

The resulting products were partially separated by chromatography on silica gel, affording the hydroxylated derivative 264 in 26% yield and a mixture of the dehydrated analogue of 264, compound 265, and the di-addition compound 266 in a combined yield of approximately 10%.



The n.m.r. spectrum of crystalline 264 in deuteriochloroform (Figure II) clearly showed that addition of one molecule of ethyl cyanoacetate to 14 had occurred, the ethyl ester signals being visible at δ 1.37 and 4.26. Moreover, addition of D_2O to the n.m.r. sample resulted in the disappearance of the hydroxyl peak at δ 4.11. The i.r. spectrum of 264 corroborated this structure assignment; besides the nitrile and carbonyl absorptions at 2260 and 1730 cm^{-1} , a broad hydroxyl stretching vibration was seen at 3525 cm^{-1} . Both the chemical analysis and mass spectrum of 264 were in accord with a hydroxylated derivative, the latter spectrum showing the typical M^+-CH_3 peak of isopropylidene sugar derivatives.³⁴¹

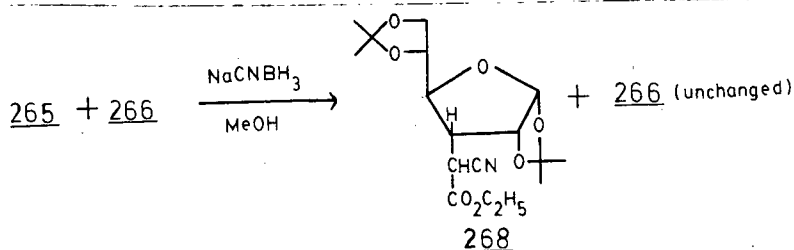
That compound 264 had the allo rather than the C-3 epimeric gluco configuration was based on previous work in our laboratory⁷² in which condensation of methyl nitroacetate with the same 3-ulose 14 in the presence of ammonium acetate gave exclusively the allo isomer, this product arising by addition of the anion from the less sterically hindered side of the ketose. More direct evidence for the allo configuration of 264 was obtained from its dilute-solution i.r. spectrum in carbon tetrachloride in which, as just mentioned, a single OH absorption peak at 3525 cm^{-1} was observed. Slessor and Tracey³⁴² have shown that the i.r. spectrum of 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose (261) under these conditions exhibits two hydroxyl peaks at 3485 and 3622 cm^{-1} , the former arising from the C-3 OH that is intramolecularly bound to the C-5 oxygen and the latter peak arising from that fraction of the C-3 OH in which C-5 and C-6 are in a rotamer that cannot be hydrogen bonded. On the other hand, the dilute-solution i.r. spectrum of the allo analogue 267 showed a single OH absorption at 3570 cm^{-1} resulting from intramolecular H-bonding with the oxygen at C-2.



The configuration at the asymmetric centre of the C-3 branched-chain of 264 was not proven though, by analogy with the reaction of methyl nitroacetate with 14, a mixture of the R and S isomers would be expected. This was indicated by the

n.m.r. spectrum of 264 (Figure II) in which minor side-bands were associated with most of the major peaks.

The mixture of the two minor reaction products 265 and 266 had an n.m.r. spectrum in deuteriochloroform that was understandably complex but from which it could nevertheless be concluded that the products in question contained the elements of ethyl cyanoacetate (263). It also seemed reasonable to assume that, based on the observed results of the Knoevenagel condensation of ethyl cyanoacetate with some non-carbohydrate ketones (see Introduction, Section 2.3.2.), this mixture probably contained the products arising, respectively, by dehydration of the initially formed addition product 264 and Michael-addition of ethyl cyanoacetate to the resulting unsaturated centre. Since compounds 265 and 266 could be separated neither by fractional crystallization nor by preparative t.l.c., recourse was made to chemical transformations to achieve separation and characterization of these components. Thus, treatment of the mixture of 265 and 266 in methanol with sodium cyanoborohydride, a reagent known^{3,4,5} to selectively reduce activated double-bonds, gave 3-C-[(R,S)-cyano(ethoxycarbonyl)methylene]-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (268) which was now easily separated by chromatography from the unreacted 3,3-C-bis-cyano(ethoxycarbonyl)methyl derivative 266. Compound 268 analyzed for a single ethyl cyanoacetate moiety, and this was substantiated by its n.m.r. spectrum in deuteriochloroform (Figure III). Moreover, this spectrum showed H-3 as a complex multiplet centred at δ 2.52, irradiation of which caused the H-2



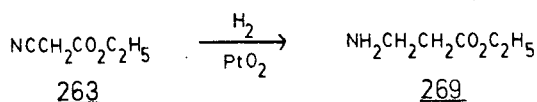
signal at $\delta 4.76$ to collapse from a multiplet to a doublet of doublets with a coupling constant ($J_{2,3}$) of 5.0 Hz. The two doublets presumably arise from an approximately 1:1 mixture of R and S isomers at the asymmetric centre of the C-3 branched-chain. Since it has been shown³⁴⁴ that trans H_2-H_3 of the furanose sugars have couplings of less than 0.5 Hz, whereas cis H_2-H_3 have couplings of greater than 2.5 Hz, then H-2 and H-3 of 268 must be in a cis orientation so that 268 has the allo configuration. The sharpness of the doublet of the anomeric proton at $\delta 5.78$ was taken as evidence that none of the alternate gluco isomer was present in the sample.

Chemical analysis and n.m.r. spectroscopy of crystalline 266 indicated that, as anticipated, this compound was the gem-di-C-alkyl derivative formed by Michael-addition of ethyl cyanoacetate to the double-bond of 265. Since no C-3 hydrogen could be seen in the n.m.r. spectrum of 266, it was concluded that addition of the second molecule of ethyl cyanoacetate had occurred at the C-3 carbon of the furanose ring of 265 rather than at the other carbon atom of the double-bond.

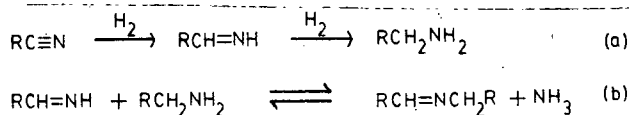
The results obtained in this Knoevenagel condensation of the 3-ulose 14 with ethyl cyanoacetate (263) are to be contrasted with those concurrently obtained by Ali and Szarek¹⁹¹ who reacted these two compounds in benzene using aqueous potassium hydroxide as base under phase transfer conditions. In this case, it was reported that only the unsaturated derivative 265 was obtained. The yield was 85%.

1.1.3. Catalytic Hydrogenation of 3-C-[(R,S)-Cyano(ethoxycarbonyl)methylene]-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (264).

Reduction of the nitrile group of the hydroxylated branched-chain sugar 264 was the next crucial step in the planned synthesis of sugar derivatives of β -alanine. Alkyl cyanides have been reduced by metal hydrides³⁴⁵, by diborane³⁴⁶ and by catalytic hydrogenation.^{161-162 347-348} Only the latter method seemed compatible with the presence of the ester functionality of compound 264. Of the catalysts that have been used for hydrogenation of nitriles, Raney nickel seemed the least attractive since it required both high pressures and temperatures.³⁴⁷ The catalytic reduction of a cyanomethyl branched-chain sugar³⁴⁹ using 5% rhodium-on-alumina³⁴⁸ has been reported to give the corresponding aminoethyl derivative. More directly applicable was the utilization by Weygand¹⁶¹ of platinum oxide (Adam's catalyst) for hydrogenation of ethyl cyanoacetate (263) to ethyl β -alanate (269).



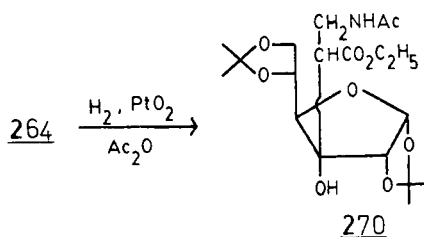
The catalytic hydrogenation of nitriles is hampered by the formation of intermediate imines (Scheme 7, Equation (a)) which can react with the amine product to form dimers³⁴⁸ (Equation (b)). Side reactions of this sort can be prevented by conducting the hydrogenation in an ammonia-saturated solution³⁴⁸, in which case the equilibrium of Equation (b) is reversed, or by trapping the primary amine as it is formed, preventing its further



Scheme 7

reaction. Either mineral acid³⁵⁰ or acetic anhydride can accomplish the latter.

Thus, since compound 264 contains both acid-sensitive isopropylidene groups and a base-sensitive ester group, its hydrogenation was attempted in anhydrous acetic anhydride using platinum oxide as catalyst at a pressure of 3 atmospheres. After 10 hours at room temperature, the N-acetamido derivative 270 was

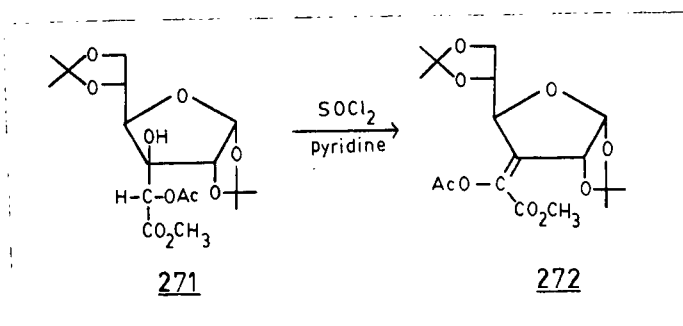


obtained in 96% yield by chromatography on silica gel. The presence of peaks at 1725 and 1750 cm^{-1} in the i.r. spectrum of 270 verified that there were two carbonyl groups in this compound while the n.m.r. spectrum of 270 in deuteriochloroform showed the required two D_2O -exchangeable protons, the NH and OH signals appearing, respectively, as a broad doublet centered at $\delta 6.35$ and a singlet at $\delta 5.12$. The methyl group of the N-acetate gave rise to two singlets around $\delta 1.90$, a reflection of the probable existence of approximately equal quantities of R and S isomers of the blocked amino acid. Additional proof of structure of 270 came from its low resolution mass spectrum in which the molecular ion peak was seen at m/e 417.

1.1.4. Dehydration of 3-C-[(R,S)-Cyan(ethoxycarbonyl)methylenel]-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (264).

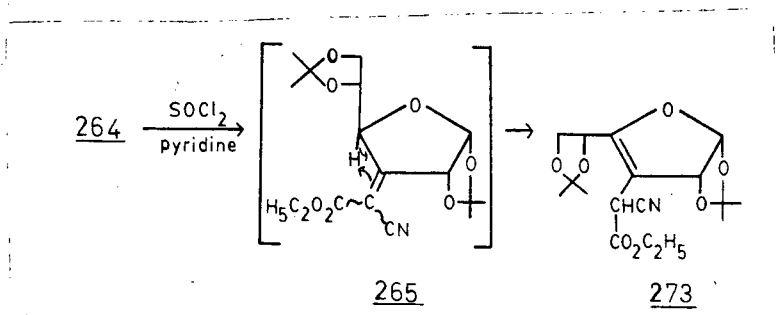
Compound 270 is a blocked Type A branched-chain sugar, the β -alanine moiety being attached to a carbon bearing a hydroxyl group. The Type B branched-chain analogue of 270, that is, the 3-deoxy derivative, was accessible by catalytic reduction of the nitrile group of compound 268. However, because this compound was available only from the minor product 265 obtained in an impure state by reaction of ethyl cyanoacetate with 3-ulose 14, dehydration of the major product 264 of this reaction seemed a more viable route to the desired Type B sugar.

A stereoselective dehydration of the C-3 branched-chain sugar 271 using thionyl chloride in pyridine has been reported by Rosenthal and Shudo⁶⁸ to give the unsaturated derivative 272,



trans elimination of the hydrogen and the hydroxyl group being favoured. This procedure was applied to 264. Thus, treatment of the latter compound with thionyl chloride in pyridine at 0° for 3 minutes gave, before work-up, a strongly fluorescent product of identical R_f on silica gel as the dehydrated compound 265. However, after work-up, the reaction showed a loss of fluorescence though its R_f had not changed. That this product,

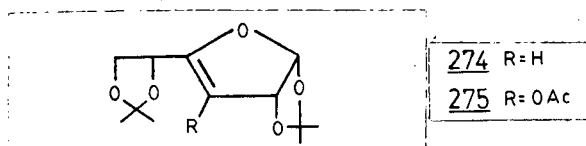
isolated by chromatography on silica gel, was 3-C-[(*R,S*)-cyano(ethoxycarbonyl)methylene]-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-erythro-hex-3-enofuranose (273) and not the expected compound 265 was indicated by its i.r. spectrum which showed a non-conjugated olefinic absorption at 1698 cm^{-1} and by its n.m.r. spectrum in deuteriochloroform which exhibited a triplet for H-5 centered at $\delta 4.72$. Neither spectra showed evidence of a hydroxyl group. Furthermore, compound 273 was not reduced by sodium cyanoborohydride, as was compound 265, and the



u.v. spectrum of 273 in methanol, which showed maxima at 212 and 263 nm did not correspond to the known absorbance of a double bond in conjugation with the ethyl cyanoacetate group, the latter system having a maximum at 228 nm.³⁵²

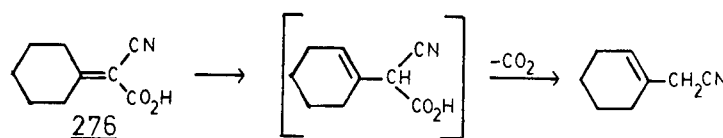
Though the *R:S* ratio of 273 could not be estimated from its n.m.r. spectrum in deuteriochloroform, use of perdeuterobenzene as the n.m.r. solvent unambiguously showed a 3:2 mixture of isomers with H-1, H-2 and methine proton of the ethyl cyanoacetate moiety of each isomer clearly resolved (Figure IV).

A few examples (274³⁵³ and 275³⁵⁴) of 3,4-unsaturated furanoses have been reported, the physical characteristics of which resemble those of compound 273. It is likely, then, that the latter compound is the result of an acid-catalyzed isomerization of the initially formed exocyclic double-bond of



265. This would account for the change in fluorescence of the reaction product after work-up, enough acid being generated by hydrolysis of the thionyl chloride during this procedure to cause the rearrangement. Direct elimination of the C-3 hydroxyl and C-4 hydrogen of 264 to give 273 is unlikely since these two groups are cis to each other.

A similar acid-catalyzed rearrangement of an exocyclic double-bond to the β - γ position was observed in the decarboxylation of the cyanoacetic acid derivative 276.³⁵⁶

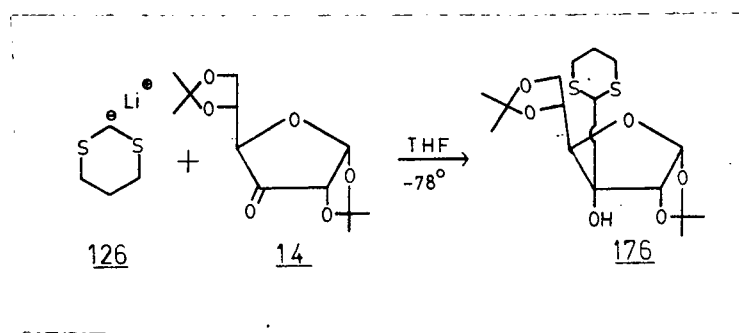


1.2 Synthesis of Derivatives of Glycos-3-yl Glycine:

Application of the Bucherer Procedure via Condensation of 1,3-Dithiane Anion with a 3-Ulose.

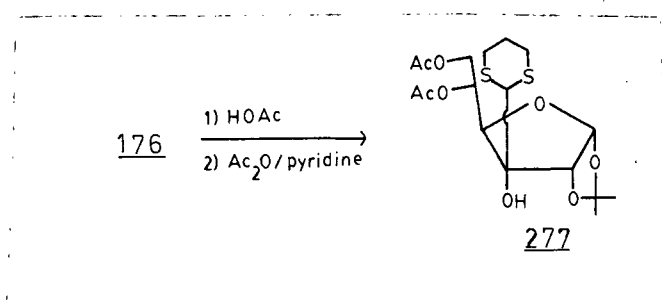
1.2.1. 3-C-(1,3-Dithian-2-yl)-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (176).

Reaction of 2-lithio-1,3-dithiane (126)¹⁹² with 1,2:5,6-di-O-isopropylidene- α -D-ribo-hexofuranos-3-ulose (14)³³⁹ in tetrahydrofuran at -78° gave the 3-C-dithianyl adduct 176 in 57% yield. Compound 176 was identical to that prepared and characterized by Paulsen and coworkers.²³⁶



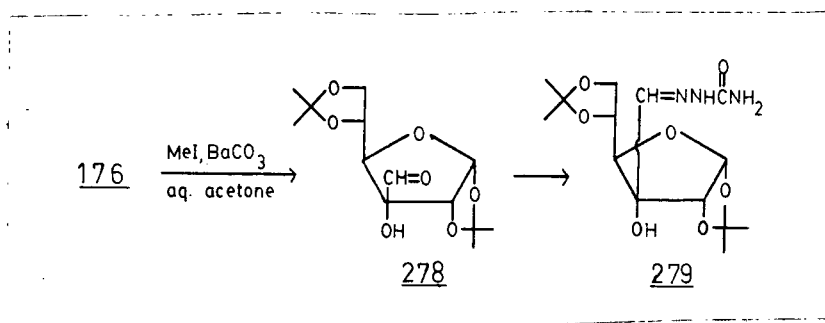
1.2.2. 3-C-Formyl-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (278) and its Semicarbazone (279).

Paulsen and Stenzel¹³⁵⁷ converted the di-O-isopropylidene derivative 176 to the 5,6-di-O-acetate 277 before hydrolyzing the dithioacetal with boron trifluoride etherate, presumably to avoid partial unblocking of the sugar during the latter step. Since acetate blocking groups would not withstand the strongly



basic conditions of our anticipated Bucherer hydantoin synthesis¹³⁹⁻¹⁴⁰ on C-3, hydrolysis of the dithioacetal was attempted on compound 176 directly by the method of Fétizon and Jurion.²³¹ Thus, a solution of 176 in aqueous acetone containing barium carbonate and methyl iodide was heated at 55° for 12 hours. The reaction was monitored by t.l.c. which showed that formation of the aldehyde (278) was accompanied by the

production of a substantial quantity of polar, base-line material. The latter was removed by aqueous work-up of the reaction mixture, giving the pure 3-C-formyl derivative 278 as a syrup in 92% yield. The n.m.r. of 278 in deuterochloroform exhibited a typical low-field (δ 9.86) signal for the aldehydic proton while the i.r. spectrum of this compound showed a strong carbonyl absorption at 1720 cm^{-1} , indicating that the formyl group had not formed an acetal during the hydrolysis.³⁵⁷ Full



characterization of 278 was achieved by its conversion to the crystalline semicarbazone derivative 279. Besides analyzing properly, semicarbazone 279 had an n.m.r. spectrum in dimethyl sulfoxide- d_6 consistent with the assigned structure, showing signals for four D_2O -exchangeable protons and one low-field (δ 7.12) imine proton, all as singlets.

1.2.3. 3-C-(2,4-diketotetrahydroimidazol-5-(R,S)-yl)-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (280).

The 3-C-formyl sugar 278 was converted to the hydantoin (also known as 2,4-diketotetrahydroimidazole) derivative 280 by the method of Bucherer, as modified by Hoyer.¹⁴² Thus, a

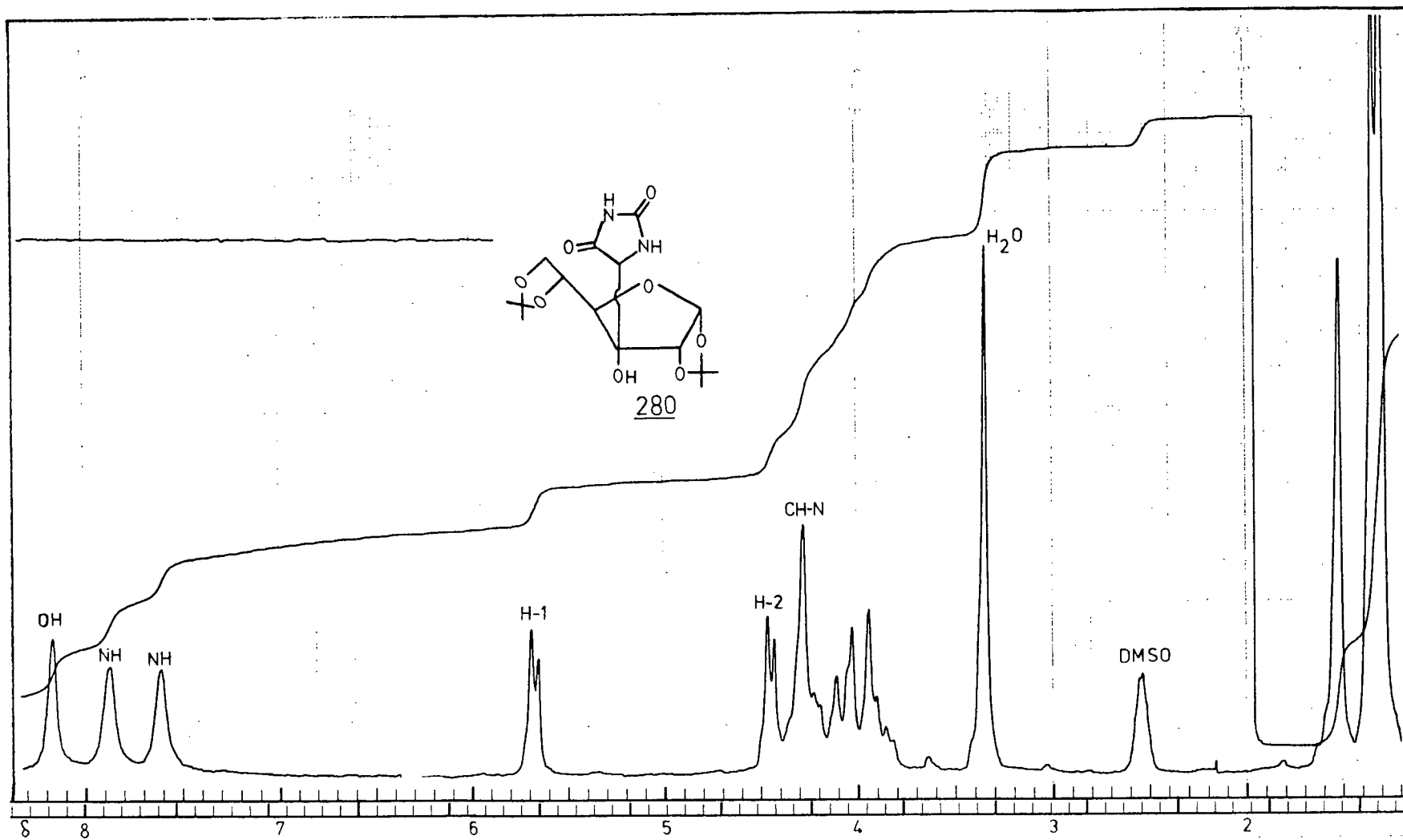
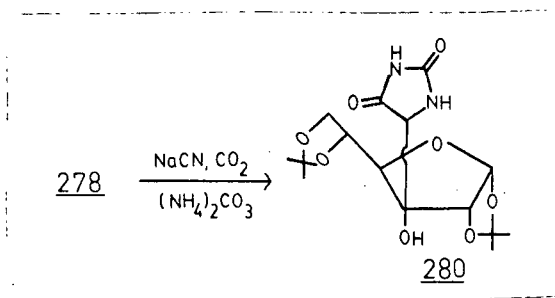


Figure V. Partial 100 MHz PMR Spectrum of 3-C-(2,4-Diketotetrahydroimidazol-5-(R,S)-yl)-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (280) in DMSO-d₆.

solution of 278 in methanol containing 4 equivalents each of sodium cyanide and ammonium carbonate was stirred for 3 hours at room temperature under 3 atmospheres of carbon dioxide. The temperature was then gradually raised to 50° and reaction continued for 12 hours. After aqueous work-up, 280 was obtained in crude form, but was purified by chromatography on silica gel and by recrystallization. The i.r. spectrum of 280 showed the

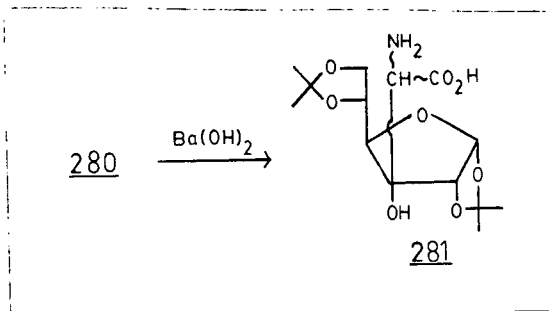


required two carbonyl absorption peaks at 1700 and 1780 cm^{-1} as well as a sharp NH signal at 3400 cm^{-1} superimposed over the broad hydroxyl band. The n.m.r. spectrum of 280 in dimethyl sulfoxide- d_6 (Figure V) showed three low-field, D_2O -exchangeable singlets, attributed to the two non-equivalent NH protons of the hydantoin ring and the hydroxyl proton of C-3.

1.2.4 L-2 and D-2-(1,2:5,6-Di-O-isopropylidene- α -D-allofuranos-3-yl)glycine (281).

When the 3-C-hydantoin sugar derivative 280 was refluxed in concentrated aqueous barium hydroxide solution for 4 hours, a ninhydrin-positive material was produced which was purified by chromatography on weakly-acidic cation exchange resin. That this compound was the 3-C-glycine branched-chain sugar 281 was demonstrated by comparison to authentic samples of this substance previously prepared by Rosenthal and Cliff³⁵⁸ via the

methyl nitroacetate route. Both compounds exhibited identical i.r. spectra and R_f 's on paper. The presence of two separate



n.m.r. signals for the anomeric proton of 281, each observed as a doublet, was evidence that this compound was, as expected, a mixture of the D- and L-amino acids. Since Rosenthal and Cliff³⁵⁸ have shown that the anomeric proton of the L-isomer of 281 resonates at lower field than that of the D-isomer, then integration of these two signals revealed that compound 281 obtained by the hydantoin route was a 2:1 mixture of the D- and L-amino acids, respectively. A preponderance of D-isomer was also indicated by the optical rotation of 281 in water; the mixture had a rotation of 43.2° , a value closer to that of the pure D-isomer ($+25^\circ$) than of the L-isomer ($+89.2^\circ$).³⁵⁸

A small quantity of the L-glycine isomer was obtained by fractional crystallization of the syrupy 281. No other attempts were made to separate the D and L diastereomers of 281 since it has been shown³⁵⁸ that their respective methyl esters are easily separable on silica gel. Thus, in contrast to the methyl nitroacetate synthesis of 3-C-glycyl-allofuranose (281), in which mainly the L optical isomer was obtained,³⁵⁸ the present synthesis of 281 via the hydantoin precursor 280 makes the D-isomer available in practical quantities.

2. Synthetic Approaches to C-Nucleosides.

The importance of C-nucleosides, both natural and synthetic, as antitumour and antibiotic agents has been described^{19 256} (see Introduction, Section 4). The synthesis of analogues of these biologically active compounds has thus been pursued in view of producing more potent or less toxic derivatives.^{256 260} The present work describes two approaches to the synthesis of C-nucleosides. The first involves formation of novel functionalized precursors to C-nucleosides by way of either a Knoevenagel condensation or carbanion displacement of a suitable group on an appropriately derivatized sugar. The second method consists of a palladium-catalyzed condensation of a pre-formed base with a carbohydrate and is an attempt to form a C-nucleoside in one-step. No satisfactory way of directly coupling a base and a sugar by carbon-carbon bonds yet exists. These approaches are described in turn.

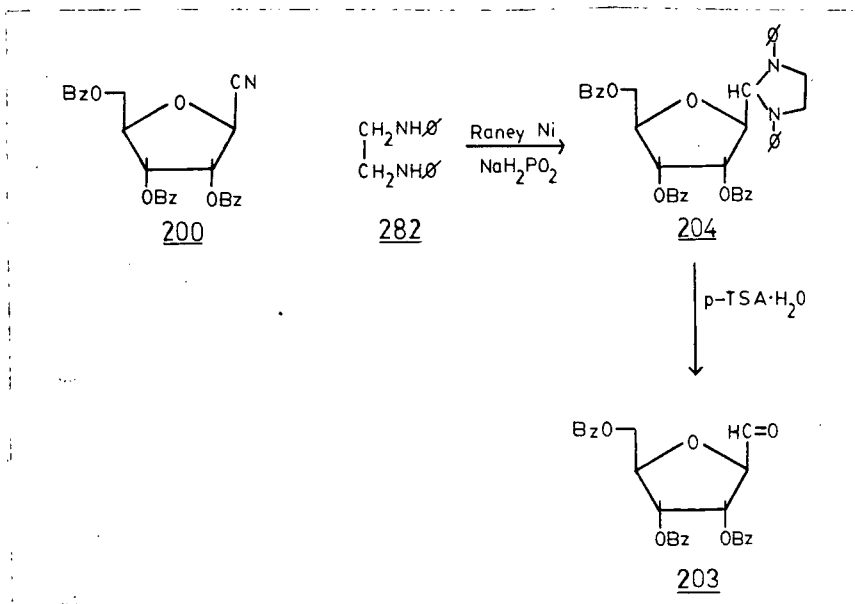
2.1. Synthesis of Functionalized Precursors to C-Nucleosides.

2.1.1. Knoevenagel Condensation of Ethyl Cyanoacetate with a 2,5-Anhydro-D_-allose.

2.1.1.1. 2,5-Anhydro-3,4,6-tri-O_-benzoyl-D_-allose (203)

Reductive hydrolysis of 2,3,5-tri-O_-benzoyl- β -D_-ribofuranosyl cyanide (200)²⁶⁷ with excess Raney nickel and sodium hypophosphite in the presence of N,N'-

diphenylethylenediamine (282) gave 1,3-diphenyl-2-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)imidazolidine (204).^{272 423} The 2,5-anhydro-D-allose 203 was then generated in high yield by treatment of the imidazolidine 204 with p-toluenesulfonic acid monohydrate in acetone.



2.1.1.2. Ethyl (E or Z)-4,7-anhydro-2-cyano-
2,3,5-trideoxy-6,8-di-O-benzoyl-D-
erythro-octon-2,4-dieneate (283).

Reaction of ethyl cyanoacetate (263) with the D-allose derivative 203 in N,N-dimethylformamide in the presence of a catalytic amount of ammonium acetate gave, as the major product, compound 283, isolated by chromatography on silica gel and further purified by recrystallization. A number of other minor, lower R_f products were formed in this reaction, as shown by t.l.c. of the mixture, but these were not characterized.

The i.r. spectrum of 283 verified the presence of an ethyl cyanoacetate moiety; peaks at 1600, 1630, 1720, and 2270 cm⁻¹ representing the ethylenic, ester carbonyl and nitrile bonds

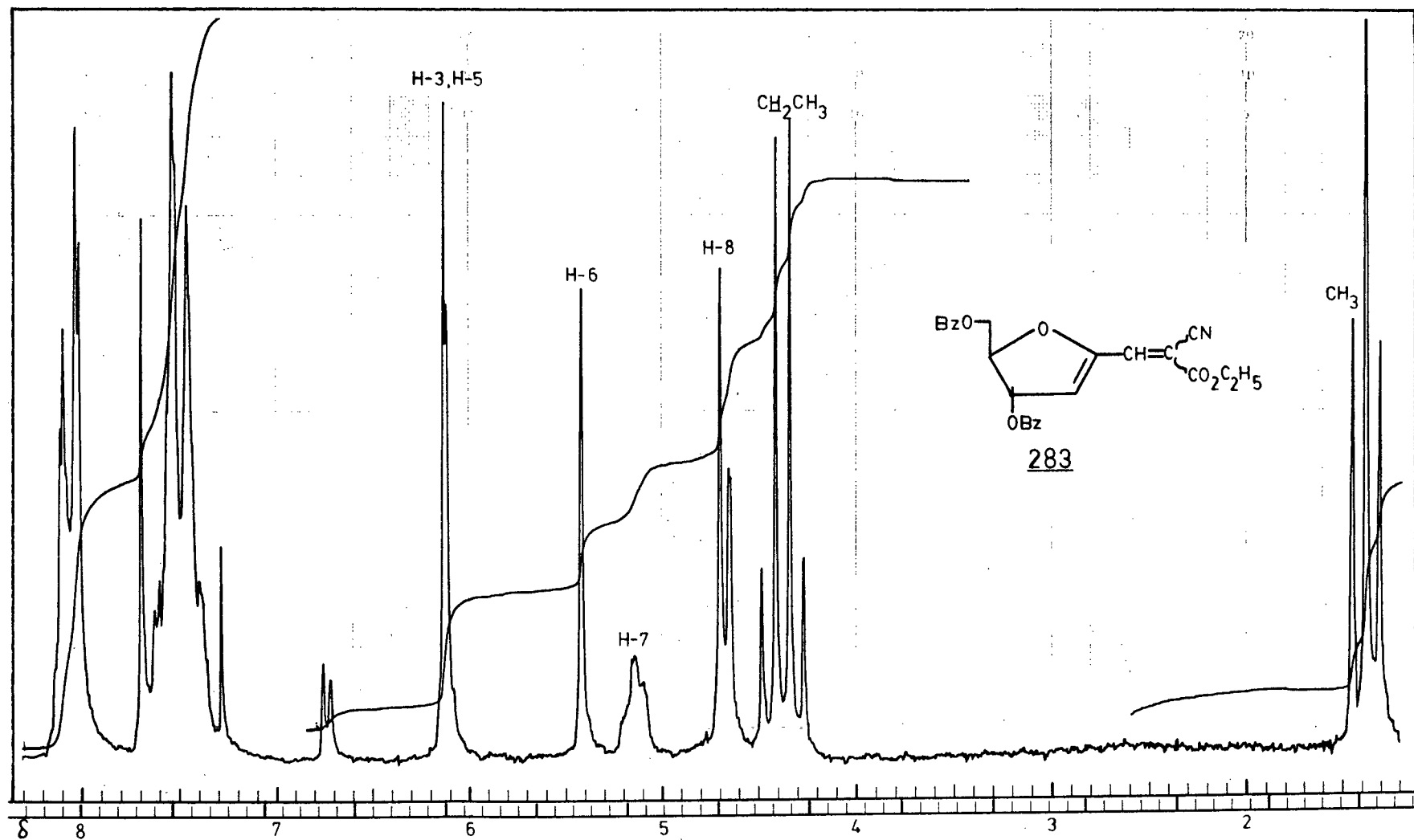
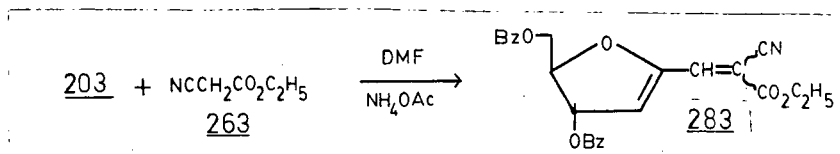


Figure VI. Partial 100 MHz PMR Spectrum of Ethyl (E or Z)-4,7-anhydro-2-cyano-2,3,5-trideoxy-6,8-di-O-benzoyl-D-erythro-octon-2,4-dieneate in CDCl_3 .



were observed. Moreover, no hydroxyl band was seen in the i.r., so that dehydration of the initially formed addition product had obviously occurred.

The n.m.r. spectrum of 283 in deuteriochloroform (Figure VI) provided the first indication that the elements of benzoic acid had been lost in the course of the reaction. This spectrum integrated for the presence of only two benzoate groups. Because of the known propensity for compound 203 to β -eliminate the benzoate group of C-3,²⁷² the position of unsaturation in the sugar ring of 283 was assigned at the C-4, C-5 position. This is also the geometry affording the greatest amount of resonance interaction. This assignment was substantiated by the n.m.r. spectrum of 283 (Figure VI), the two vinylic protons at C-3 and C-5 giving rise to superimposed signals at δ 6.12. This latter doublet collapsed to a two-proton singlet when H-6 was irradiated.

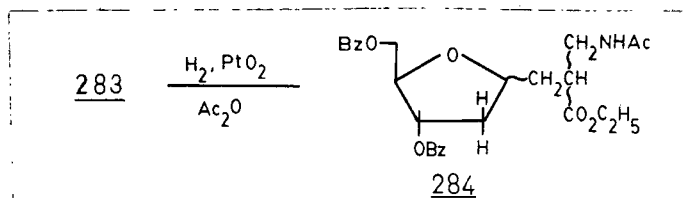
The mass spectrum and chemical analysis of 283 provided further proof that elimination of a benzoate group had occurred during the Knoevenagel condensation with 203. There was no indication by any of these methods of characterization that 283 contained more than one equivalent of ethyl cyanoacetate.

Although no attempt was made to establish whether compound 283 is the E or the Z isomer about the 2,3-double bond, previous studies¹⁸⁵⁻¹⁸⁶ of Knoevenagel condensations of ethyl cyanoacetate with non-carbohydrate aldehydes have shown that the isomer in which the two bulkiest groups are trans is favoured.

It could thus be predicted that 283 is the E isomer.

2.1.1.3. Catalytic Hydrogenation of Ethyl (E or Z)-4,7-anhydro-2-cyano-2,3,5-trideoxy-6,8-di-O-benzoyl-D-erythro-octon-2,4-dieneate (283).

Hydrogenation of compound 283 over platinum oxide in acetic anhydride, conditions previously shown to reduce a nitrile function to the corresponding acetamido derivative (see Section 1.1.3) yielded mainly the product in which both double bonds, as well as the nitrile group, were saturated (284). The i.r. spectrum of 284 no longer showed the nitrile and ethylenic absorption peaks seen in the precursor. Instead, peaks for an amide carbonyl and the associated NH were observed at 1660 and 3450 cm^{-1} respectively. The n.m.r. spectrum of 284 (CDCl_3) was consistent with a completely reduced system; no low-field vinylic protons were observed and the N-acetate signal was visible as a singlet at δ 1.95. Though the mass spectrum of 284 displayed the required molecular ion peak at m/e 497, smaller signals at m/e 503 and 509 suggested that partial reduction of the phenyl rings of the benzoate groups of 283 had also occurred. This was not reflected in the chemical analysis of 284.



Compound 284 is a precursor to the little-known class of 2-

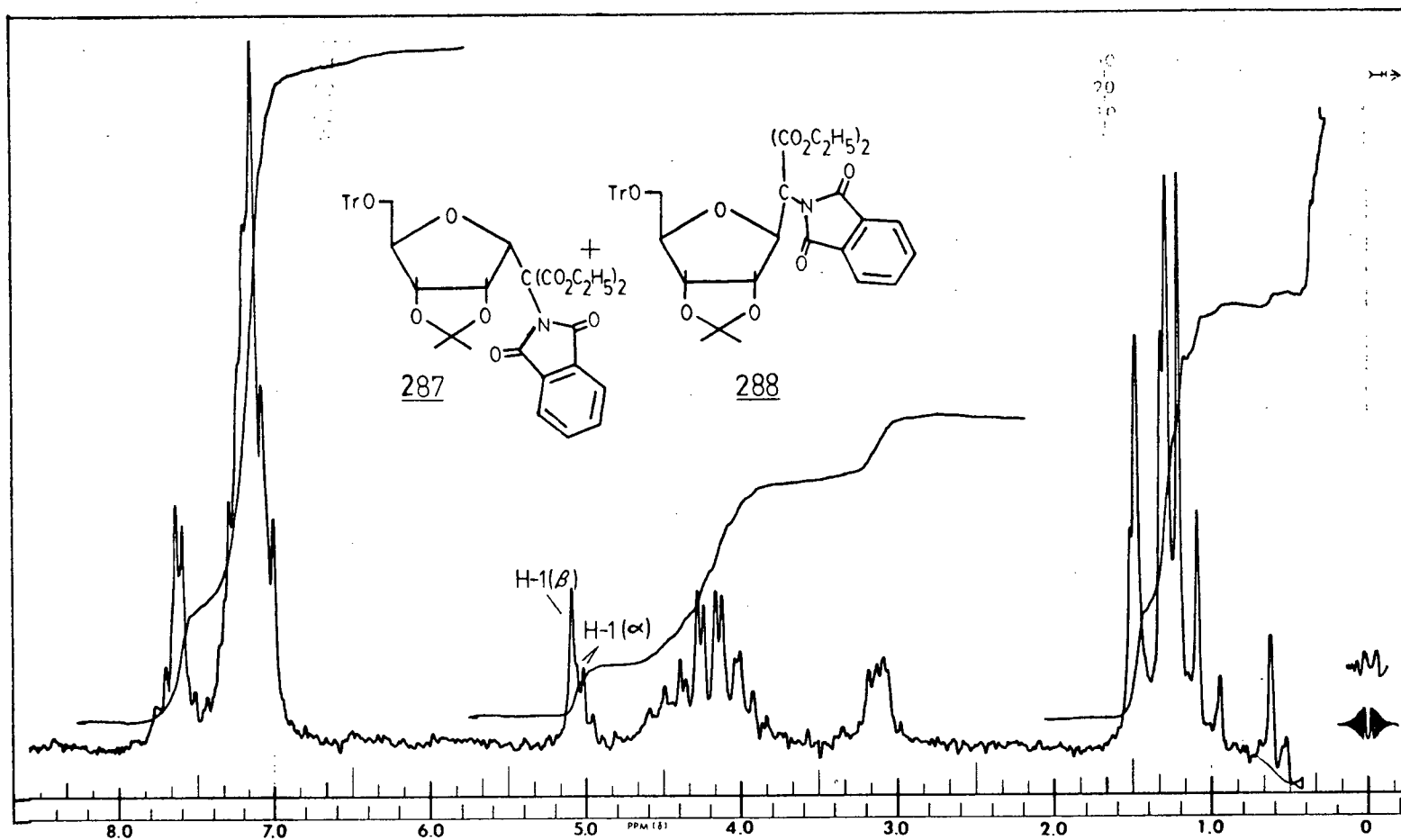


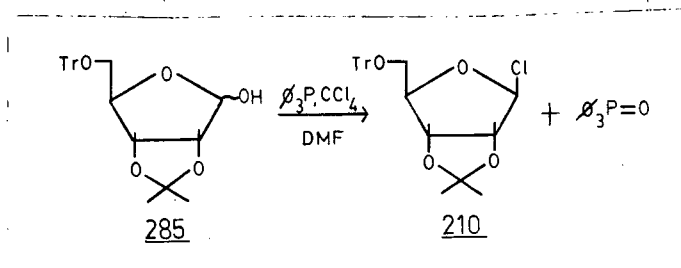
Figure VII. 60 MHz PMR Spectrum of Diethyl 2,3-O-isopropylidene-5-O-trityl- α -(and β)-D-ribofuranosyl phthalimidomalonate (287 and 288) in CDCl_3 .

deoxy-D-ribose C-nucleosides. ³⁵⁹⁻³⁶⁰

2.1.2. Condensation of Diethyl Sodium Phthalimidomalonate with a Glycosyl Halide.

2.1.2.1. 2,3-O-Isopropylidene-5-O-trityl- β -D-ribofuranosyl chloride (210).

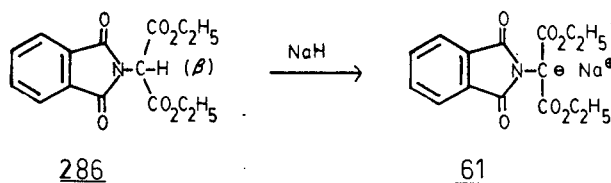
Treatment of a solution of 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose (285) ³⁶² in N,N-dimethylformamide with triphenylphosphine and carbon tetrachloride gave the corresponding β -glycosyl chloride 210.^{276 362} Though the moisture sensitive chloride 210 could be crystallized³⁶², it was more advantageous to utilize the pure syrup obtained after work-up for subsequent reactions.



2.1.2.2. Diethyl sodium phthalimidomalonate (61).

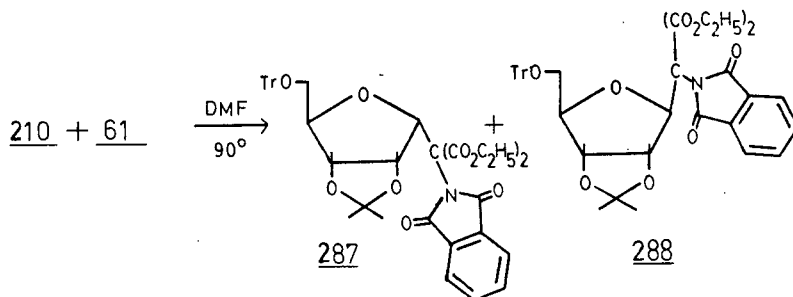
A variation of the known procedure¹²⁴ of forming the sodium salt of diethyl phthalimidomalonate (286) was employed for the present study. Thus, to a solution of 286⁴²⁰ in anhydrous ether was added one equivalent of sodium hydride. The yellow

precipitate which had formed after one hour of stirring was filtered off and shown to be the sodium salt 61 by virtue of the absence of a signal for the β -proton in its n.m.r. spectrum, taken in dimethyl sulfoxide- d_6 .



2.1.2.3. Diethyl 2,3-O-isopropylidene-5-O-trityl- α -(and β)-D-ribofuranosyl phthalimidomalonate (287 and 288).

Reaction of the β -glycosyl chloride 210 with an equivalent of diethyl sodium phthalimidomalonate (61) in anhydrous N,N-dimethylformamide for 18 hours at 90° gave a mixture of the anomeric C-glycosides 287 (α) and 288 (β) in a combined yield

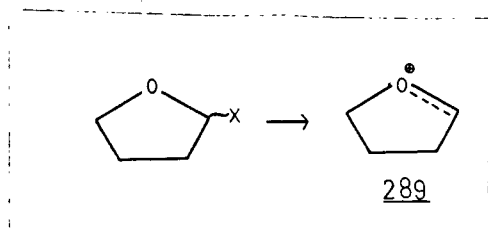


of 46%. The isomers were not separated. The n.m.r. spectrum of the mixture of 287 and 288 in deuteriochloroform (Figure VII) clearly showed the presence of the phthalimidomalonate moiety, the ethyl ester signals appearing as a triplet and a quartet at δ 1.20 and 4.20, respectively, while the phthalimido protons resonated at δ 7.65. An approximately 1:1 anomeric mixture was also indicated by the n.m.r. spectrum by the fact that the anomeric proton gave rise to a singlet and a doublet ($J_{1,2}$ 6 Hz) at δ 5.10 and 5.03, respectively. A singlet for H-1 is generally associated with trans H-1, H-2 of a furanose ring (i.e. β , 288) while a doublet with a coupling constant ($J_{1,2}$) greater than 3.5 Hz lies within the range required for a cis relationship of these protons³⁶³ (i.e. α , 287).

The n.m.r. evidence for 287 and 288 was corroborated by high resolution mass spectrometry, which exhibited the typical (M^+-CH_3) peak of isopropylidene derivatives.³⁴¹ Moreover, a glycosidic C-C bond was demonstrated by the absence of an appreciable peak at m/e 431 ($M^+-aglycon$). The O-glycosides are known to favour this fragmentation pattern.³⁶⁴ The i.r. spectrum of this C-glycoside exhibited the appropriate carbonyl absorptions at 1725 and 1755 cm^{-1} .

A simple S_N2 displacement of the chloride ion of the β -glycoside 210 by the diethyl phthalimidomalonate anion 61 would be expected to give exclusively the α -anomer 287. However, the fact that a mixture of the α and β anomers is actually formed in this reaction suggests that the mechanism has some S_N1 character. This is not unusual since nucleophilic displacements of C-1 halides of both pyranosyl³⁶⁵ and furanosyl³⁶⁶ sugars

having no participating groups at C-2 have been shown to proceed via the ring-oxygen stabilized carbonium ion 289 to give mixtures of the α and β isomers, the proportions of each being dependent on the reaction medium and the presence of added salts.

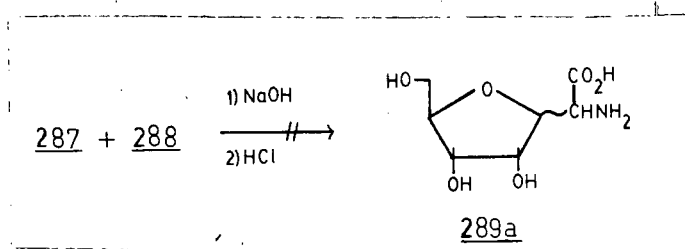


The C-glycoside 288 may be considered as a blocked derivative of β -D-ribofuranosyl glycine and, as such, is a precursor not only of the natural formycins (189-191) and pyrazomycins (192-193) but also of potentially chemotherapeutically valuable analogues of these biologically active C-nucleosides.^{19 256} The synthesis, concurrent with the present work, of a C-glycyl furanoside via condensation of a 1,4-lactone sugar with ethyl isocyanoacetate (see Introduction, Section 4.1.2., compound 216a) has been reported²⁸⁰; however, only molecules in which the amino acid and the sugar hydroxyl groups have a cis relationship are available by this route and so cannot be considered as precursors to the natural C-nucleosides.

2.1.2.4. Attempted Unblocking of 287 and 288.

An initial attempt to deprotect the C-glycosides 287 and 288 has been unsuccessful. Thus, treatment of a mixture of 287 and 288 in THF and 1N aqueous sodium hydroxide at refluxing temperatures followed by acid hydrolysis (2N HCl) of the

blocking groups of the resulting product gave triphenylcarbinol which crystallized from the reaction mixture and a ninhydrin-positive material. The latter substance was isolated by chromatography of the reaction mixture on a cation-exchange resin. However, an n.m.r. spectrum of the collected ninhydrin-positive fractions, obtained in only 16% yield, did not conclusively indicate the presence of a ribosyl moiety so that it appears that the C-glycyl ribose derivative 289a does not



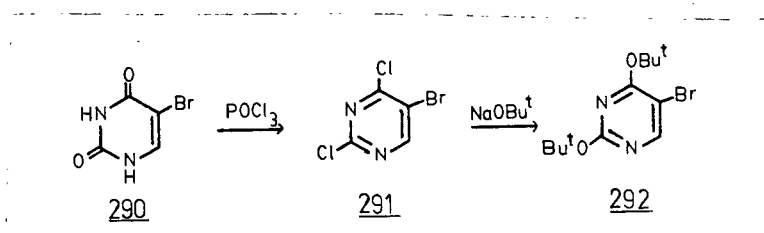
withstand the rigorous conditions required for deprotection of 287 and 288.

2.2. Synthesis of a 5-Alkyl Uracil. Attempted One-Step Synthesis of a Pseudouridine Derivative.

2.2.1. 5-Bromo-2,4-di-t-butoxypyrimidine (292)

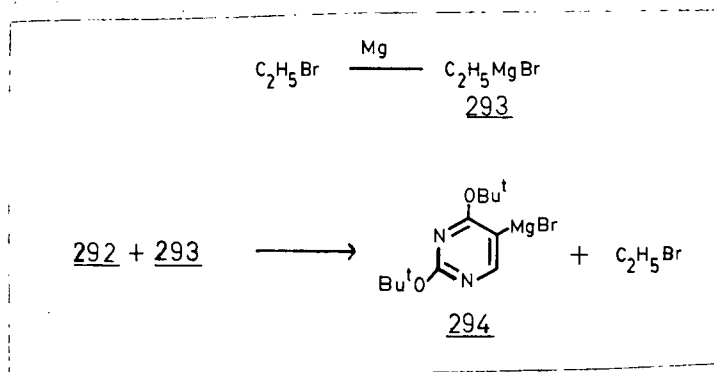
Though the use of methyl groups to block the 2- and 4-positions of 5-bromouracil (290) would have been more sterically advantageous to the introduction of substituents at C-5 of this molecule, the vigorous acidic conditions required to remove these blocking groups²⁹² did not seem attractive. Instead, 290 was protected with the more easily-hydrolyzed t-butyl group. Thus, by published procedures,³⁶⁷ 290 was first chlorinated at C-2 and C-4 using phosphorus oxychloride, yielding compound 291. Reaction of 291 with sodium t-butoxide then gave in good yield the blocked 5-bromopyrimidine 292.²⁹³ The mass spectrum of

292 exhibited the appropriate molecular ion peak.



2.2.2. 5-(1-Propen-2-yl)uracil (296) via the Grignard Reagent, 2,4-Di-*t*-butoxy-5-magnesiumbromopyrimidine (294).

The formation of Grignard reagents from 5-halouracils has not previously been reported. Our initial attempts to form the 5-bromomagnesium compound 294 by refluxing a tetrahydrofuran solution of 292 containing magnesium metal were not successful. Instead, the often-used method of entrainment³⁶⁸ was utilized, wherein ethylmagnesium bromide (293) was first formed from ethyl bromide and magnesium and which, by a presumed exchange reaction with the added 5-bromopyrimidine 292, gave the desired Grignard reagent, 294.



To show that 294 had, in fact, been formed by this procedure, acetone was added to the reaction mixture. After work-up, an i.r. spectrum of the crude reaction mixture showed a prominent absorption at 3650 cm^{-1} , a first indication that the hydroxyl compound 295 had formed. Compound 295 was not further

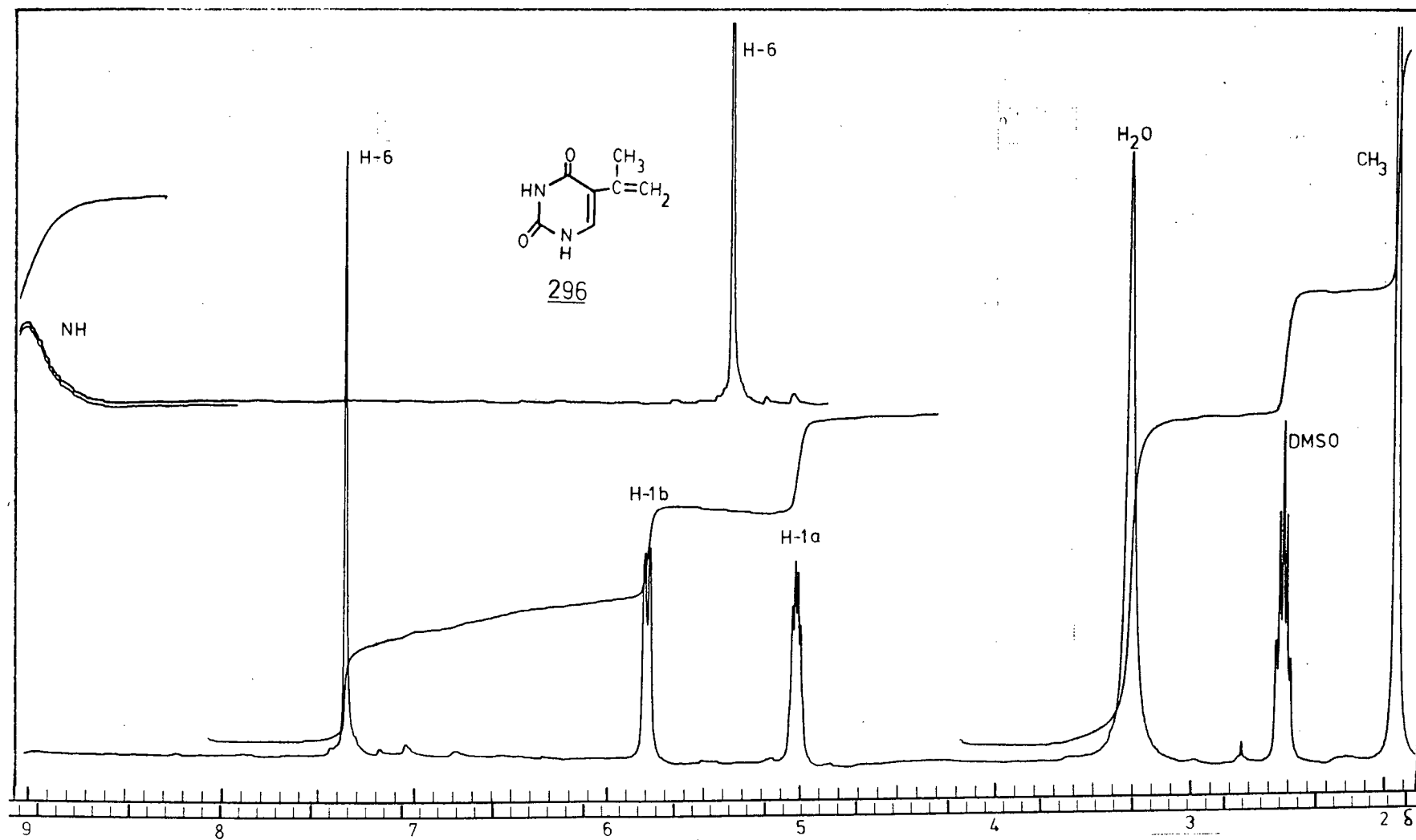
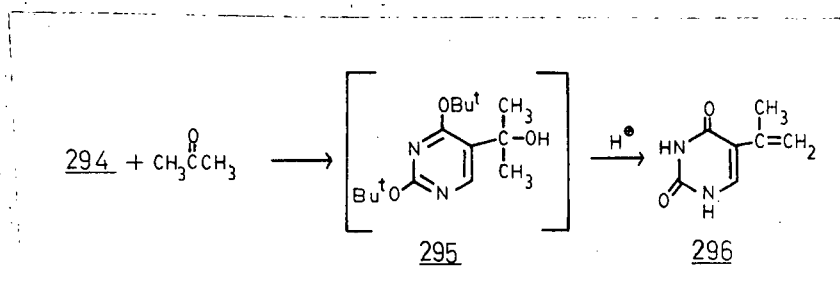
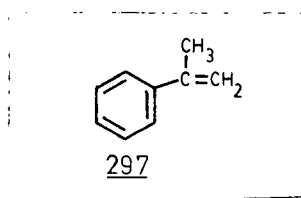


Figure VIII. Partial 100 MHz PMR Spectrum of 5-(1-Propen-2-yl)uracil (296) in DMSO-d₆.

characterized but was immediately unblocked with ⁴ dilute, methanolic hydrochloric acid to give the 5-alkenyluracil 296.



That 295 had undergone dehydration during the acid treatment was obvious from the n.m.r. of the product 296 (Figure VIII). This spectrum greatly resembled that of α -methyl styrene³⁶⁹ (297) in that a peak corresponding to only one methyl group was seen at δ 1.92, while the two vinylic protons of the side-chain were visible at δ 5.01 (two doublets) and 5.79 (doublet). The proton at C-6 gave rise to the expected low-field singlet (δ 7.35). Although the chemical analysis of 296 was not entirely satisfactory, the mass spectrum of this compound was unambiguous, a strong molecular ion peak at m/e 152 being observed.

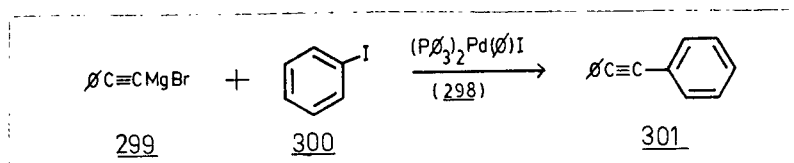


Thus, formation of 296 proved that the 5-bromomagnesium precursor 294 had indeed been generated by the procedure just described. With this in mind, the direct coupling of the Grignard reagent 294 with a blocked glycosyl halide was attempted.

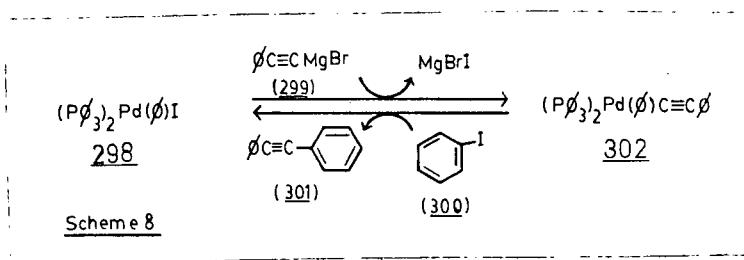
2.2.3. Attempted Coupling of 294 and a Glycosyl

Halide (210) Using a Palladium (II) Catalyst (298).

The use of palladium and its complexes to catalyze^{280a} the formation of C-C bonds has been briefly described (see Introduction, Section 5). In particular, our attention was drawn to the finding²⁹⁰ that iodo(phenyl)bis(triphenylphosphine) palladium (II) (298)³⁷⁰ could serve as a catalyst in the cross-coupling of Grignard reagents and aryl halides. Thus, phenylethynylmagnesium bromide (299) and phenyl iodide (300) reacted in the presence of catalyst 298 to give an 84% yield of diphenylacetylene (301)²⁹⁰



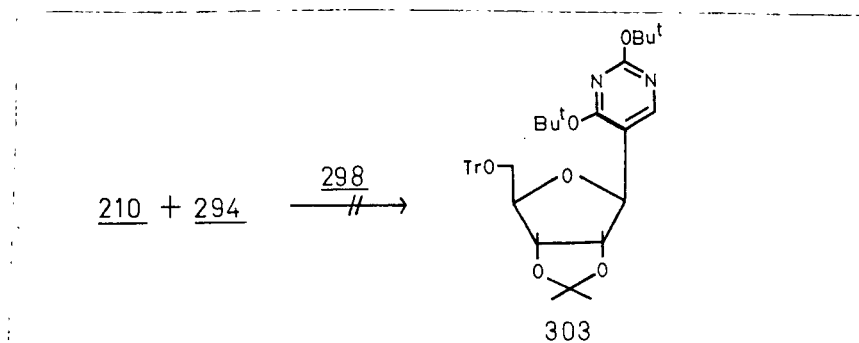
The mechanism postulated for this reaction, depicted in Scheme 8, invoked the formation of the palladium complex 302 which then reacted with phenyl iodide (300) to form 301 and



regenerate the catalyst 298.

An analogous reaction sequence, in which the pyrimidine Grignard reagent 294 replaces 299 and the glycosyl halide 210 replaces 300, was envisaged as a possible route to a one-step synthesis of blocked pseudouridine (303). Accordingly, a solution of the Grignard reagent 294 in THF was added to a refluxing solution of the ribofuranosyl chloride 210²⁷⁶

containing a catalytic amount of the palladium complex 298. However, even after 12 hours refluxing of this reaction mixture, no cross-coupled products resembling 303 could be discerned from an examination by n.m.r. of the several fluorescent reaction



components isolated by chromatography.

A possible explanation for the failure of this reaction may lie in the inability of the glycosyl halide 210 to bind effectively with the catalyst. Self-condensation of the Grignard reagent 294 could also be a factor.

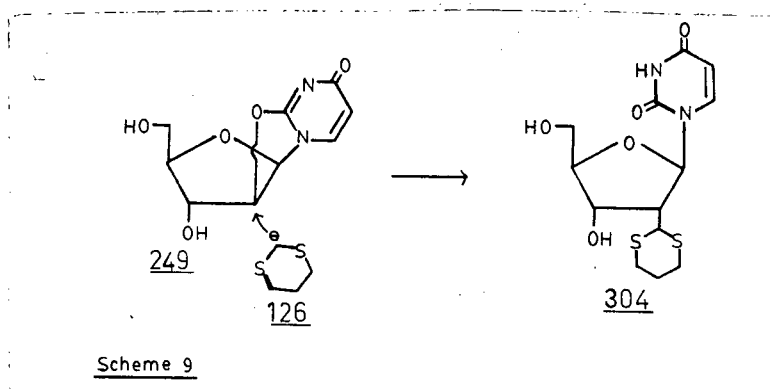
This approach to the synthesis of C-nucleosides was abandoned with the publication by Arai and Daves²⁹⁵ of a related, but successful, palladium-catalyzed C-C coupling of a pyrimidine and a sugar (see Introduction, Section 5.1.). Nevertheless, the present work has resulted in a new method of alkylating the C-5 position of uracil (e.g. 296).

3. Modifications of the 2- and 6- Positions of Uridine Using 1,3-Dithiane Anion.

The work to be presently discussed was originally undertaken in an attempt to introduce functionalized C-C- linked substituents at the C-2 position of the sugar moiety of the natural nucleosides. Examples of so-modified nucleosides, either

natural or synthetic, are not numerous and so, in view of the known biological activities¹⁹ of the C-3' and C-5' modified nucleosides (e.g. puromycin (28) and the polyoxins (29), respectively) the development of a practical synthetic route to these C-2' analogues seemed justified.

Inspired by the work of Yamashita and Rosowsky²⁵², who demonstrated that the anion of 1,3-dithiane (126) attacked regioselectively at C-2 of the 2,3-epoxide sugar 184 (see Introduction, Section 3.3.3.) and, knowing that certain nucleophiles (e.g. azide³¹², phthalimide³¹³) also attack at C-2 of the sugar moiety of 2,2'-anhydrouridines (249) to give C-2' modified nucleosides (251), then it seemed reasonable to expect that the dithiane anion 126 would react with the anhydronucleoside 249 to form 304 (Scheme 9), thereby yielding



the desired C-2'-functionalized nucleoside.

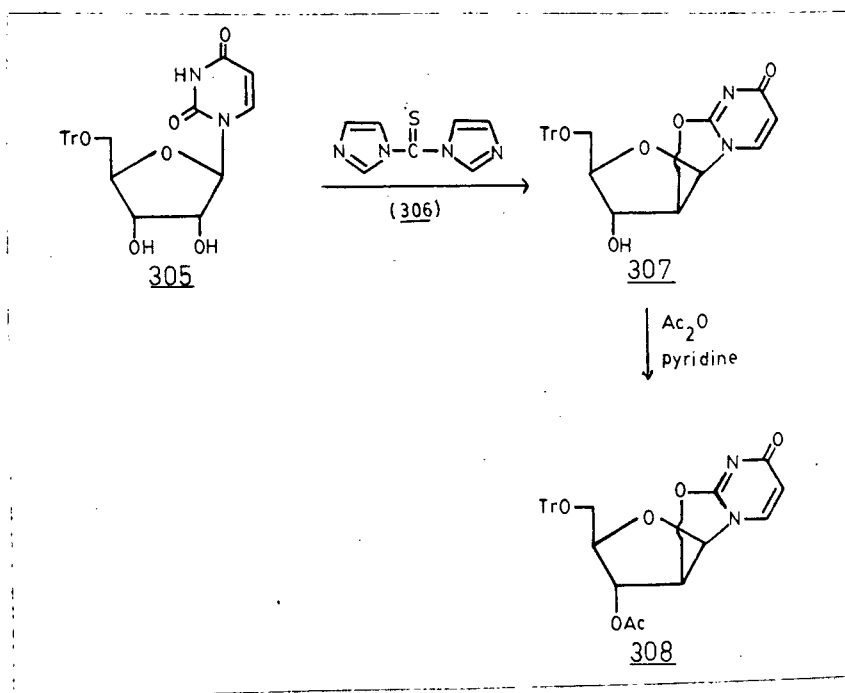
The reaction of 249 and 126 did not, as described in the following section, proceed as expected, but rather yielded a novel method of modifying the equally interesting and little-studied C-2 and C-6 positions of the nucleoside. This experiment was subsequently altered, as described in Section 3.2. to allow the attachment of an amino acid at C-6 of uridine, thereby

extending our previous work (Section 1) on the synthesis of glycosyl amino acids (also, see Introduction, Section 6 for a discussion of base-modified nucleosides).

3.1 Reaction of 1,3-Dithiane Anion with a 2,2'-Anhydronucleoside: Functionalization of the 2- and 6- Positions of Pyrimidine Nucleosides.

3.1.1. 2,2'-Anhydro-1-(3-O-acetyl-5-O-trityl- β -D-arabinofuranosyl)uracil (308).

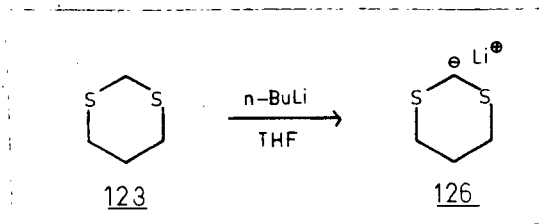
Reaction of 5'-O-trityluridine (305)³⁷³ with one equivalent of thiocarbonyldiimidazole (306) in refluxing toluene gave, in almost quantitative yield, crystalline 2,2'-anhydro-1-(5-O-trityl- β -D-arabinofuranosyl)uracil (307).³⁷⁴ Compound 307 was then treated with acetic anhydride in pyridine to afford the 3'-O-acetyl derivative 308. The synthesis of 308 has been



reported³⁷⁵ though no physical constants were given.

3.1.2. 2-Lithio-1,3-Dithiane (126).

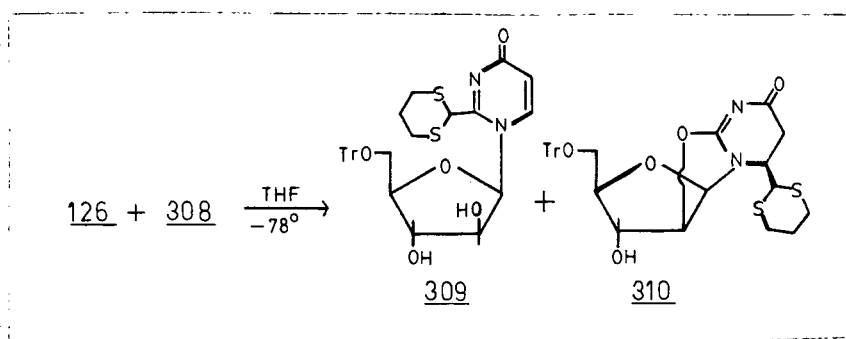
Reaction of 1,3-dithiane (123) in anhydrous tetrahydrofuran (THF) with an equivalent of n-butyllithium in hexane at -78° under nitrogen gave the anion 126¹⁹². The anion solution was generally stored at -20° for 2-5 hours prior to use.



2.1.3. Synthesis of 2-(1,3-Dithian-2-yl)-1-(5-O-trityl- β -D-arabinofuranosyl)-4(1H)-pyrimidinone (309) and 2,2'-Anhydro-5,6-dihydro-6-(S)-(1,3-dithiane-2-yl)-1-(5-O-trityl- β -D-arabinofuranosyl)uracil (310).

When a solution of the blocked anhydronucleoside 308 in anhydrous THF was added to a 5 molar excess of the anion 126 in THF at -78° , two major products could be discerned by t.l.c. after one hour of reaction. Column chromatography on silica gel of the worked-up reaction mixture afforded the two products 309 and 310 in yields of 15 and 30%, respectively. The elucidation of the structures of 309 and 310 will be discussed in turn.

The n.m.r. spectrum of 309 in dimethyl sulfoxide- d_6 showed, besides the high-field signals for the hydrocarbon protons of the dithiane moiety, two D_2O -exchangeable protons as doublets at δ 5.71 and 5.92. These were attributed to the C-2' and C-3' secondary hydroxyl groups, the C-3' hydroxyl simply resulting from hydrolysis of the acetate group of 308 under the basic



conditions of the reaction.

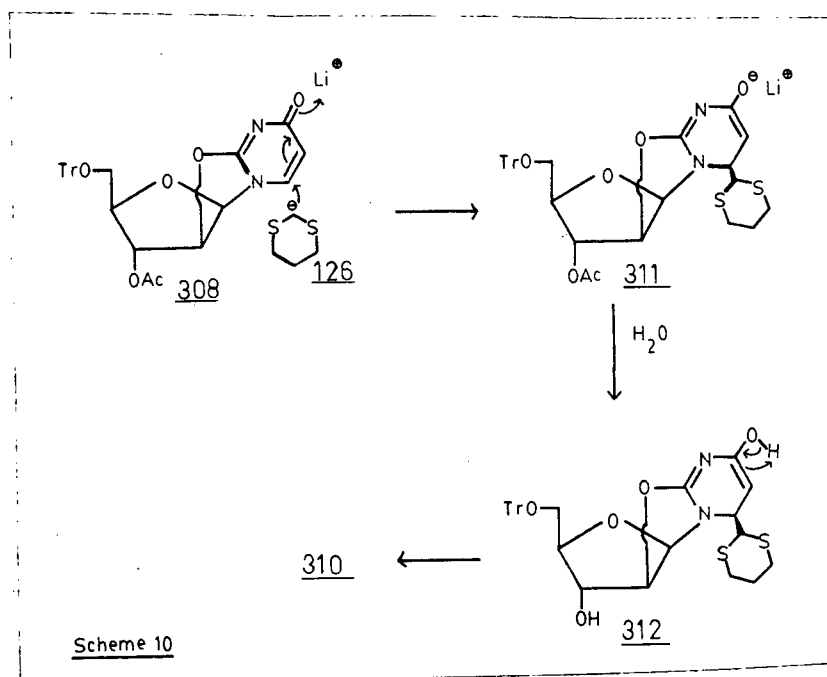
Moreover, the proton at the 2-position of the dithiane ring (i.e. S-CH-S) gave rise to a sharp singlet observed at δ 5.46, downfield from its usual position of $\sim \delta$ 4.3, possibly due to its proximity to the unsaturated imine. The latter group, as well as the olefinic bond of 309, absorbed in the appropriate region in the infrared (1635 and 1600 cm^{-1} , respectively). Though a molecular ion (M^+) peak was not observed in the mass spectrum of 309, the characteristic signal arising from cleavage of the glycosidic carbon-nitrogen bond³⁷⁶ was seen at m/e 375. This corresponds to the loss of 2-(1,3-dithian-2-yl)-4-pyrimidinone, that is, M^+ -base, and proved that the dithiane group was not bonded to the sugar moiety. This spectral data, as well as the chemical transformations of 309 (described below, Sections 3.1.4-3.1.6), established that this compound was that arising by attack of the dithianyl anion 126 at C-2 of the anhydronucleoside 308 with concomitant generation of an arabino sugar moiety. Based on the results of the action of other nucleophiles³¹⁰⁻³¹¹ on anhydronucleosides, the formation of the C-2 dithianyl adduct 309 from 308 and 126 was not unexpected (see Introduction, Section 6.2.1.).

The structure of the second major product (310) obtained by reaction of 308 and 126 was established by n.m.r. and

i.r. spectroscopy. Firstly, the n.m.r. of 310 in deuteriochloroform showed, in contrast to that of 309, only one D₂O-exchangeable hydroxyl proton (δ 5.50) and, significantly, disappearance of the low-field H-5 and H-6 doublets of the pyrimidine ring, with generation of a two-proton multiplet in the δ 2.64-3.26 region (H-5), partially obscured by the large dithiane resonances. This n.m.r. spectrum was thus consistent with a pyrimidine nucleoside in which the 5,6-double bond was saturated.^{319 377} Moreover, the H-1' and H-2' resonances at δ 6.25 and 5.18, respectively, and their coupling constant of 5.0 Hz corresponded with the values obtained by Hall and coworkers³⁷⁷ for these protons in the only other known report of the synthesis of C-6 substituted 2,2'-anhydro-5,6-dihydropyrimidine nucleosides (see Introduction, Section 6.2.2.3. compound 260). The i.r. spectrum of 310 also showed absorbances characteristic of an O-C=N-C=O system,³⁷⁷ with peaks at 1702, 1595 and 1460 cm⁻¹.

The formation of compound 310 can be rationalized (Scheme 10) by invoking a 1,4-Michael-type addition of the dithiane anion 126 to the unsaturated carbonyl system of anhydronucleoside 308 to give the lithium salt 311. Upon aqueous work-up, the enol 312 forms which tautomerizes to the stable dihydro derivative 310.

Although the 5,6-double bond of uridine derivatives is known to be susceptible to such 1,4-additions by various nucleophiles to give the corresponding 6-substituted-5,6-dihydro compounds,^{303 319-320} the behaviour of the dithiane anion 126 in this respect was somewhat unexpected since this anion has been



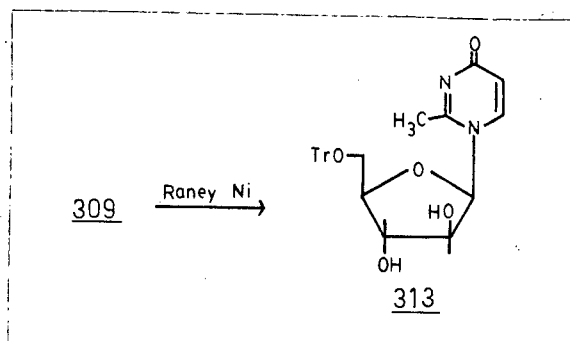
generally observed¹⁹⁹ to give only non-conjugate 1,2-addition products in reactions with α,β -unsaturated carbonyl systems (see Introduction, Section 3.1).

Thus, in addition to the modification of pyrimidine nucleosides at C-2 (i.e., 309), facile functionalization at C-6 of these nucleosides appeared feasible in view of the possibility of converting the dithiane moiety of 310 to a formyl group.¹⁹² With this in mind, the chemical properties of compounds 309 and 310 were studied. The results are reported in the following sub-sections.

3.1.4. Desulfurization of 309 to Give 2-Methyl-1-(5-O-trityl- β -D-arabinofuranosyl)-4(1H)-pyrimidinone (313).

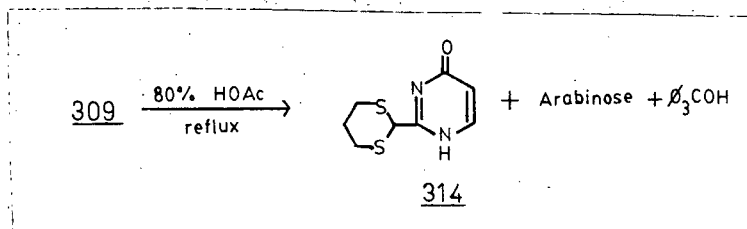
Treatment of the C-2 dithianyl nucleoside 309 with activated Raney nickel³⁷⁸ in ethanol at refluxing temperatures gave the 2-methyl derivative 313. Compound 313 had the same

physical characteristics as that prepared by Kunieda and Witkop³¹¹ and thus provided unambiguous proof of structure of the precursor, 309.



3.1.5. Acid Hydrolysis of 309.

It was found that the nucleoside 309 could be easily degraded in refluxing acetic acid to the corresponding free base, 2-(1,3-dithian-2-yl)-4-pyrimidinone (314), obtained in a crystalline state by addition of ethanol to the reaction mixture. The chemical analysis and n.m.r. spectrum of 314 were completely consistent with the proposed structure. The sugar moiety of 309 was proven to be D-arabinose by comparison of R_f values on paper of the sugar component produced by hydrolysis of 309 with authentic arabinose.



3.1.6. Detritylation of 309 to Give 2-(1,3-Dithian-2-yl)-1-β-D-arabinofuranosyl-4(1H)-pyrimidinone (317).

Detritylation of 309 to give the corresponding unblocked nucleoside was hampered by the extreme acid-lability of the

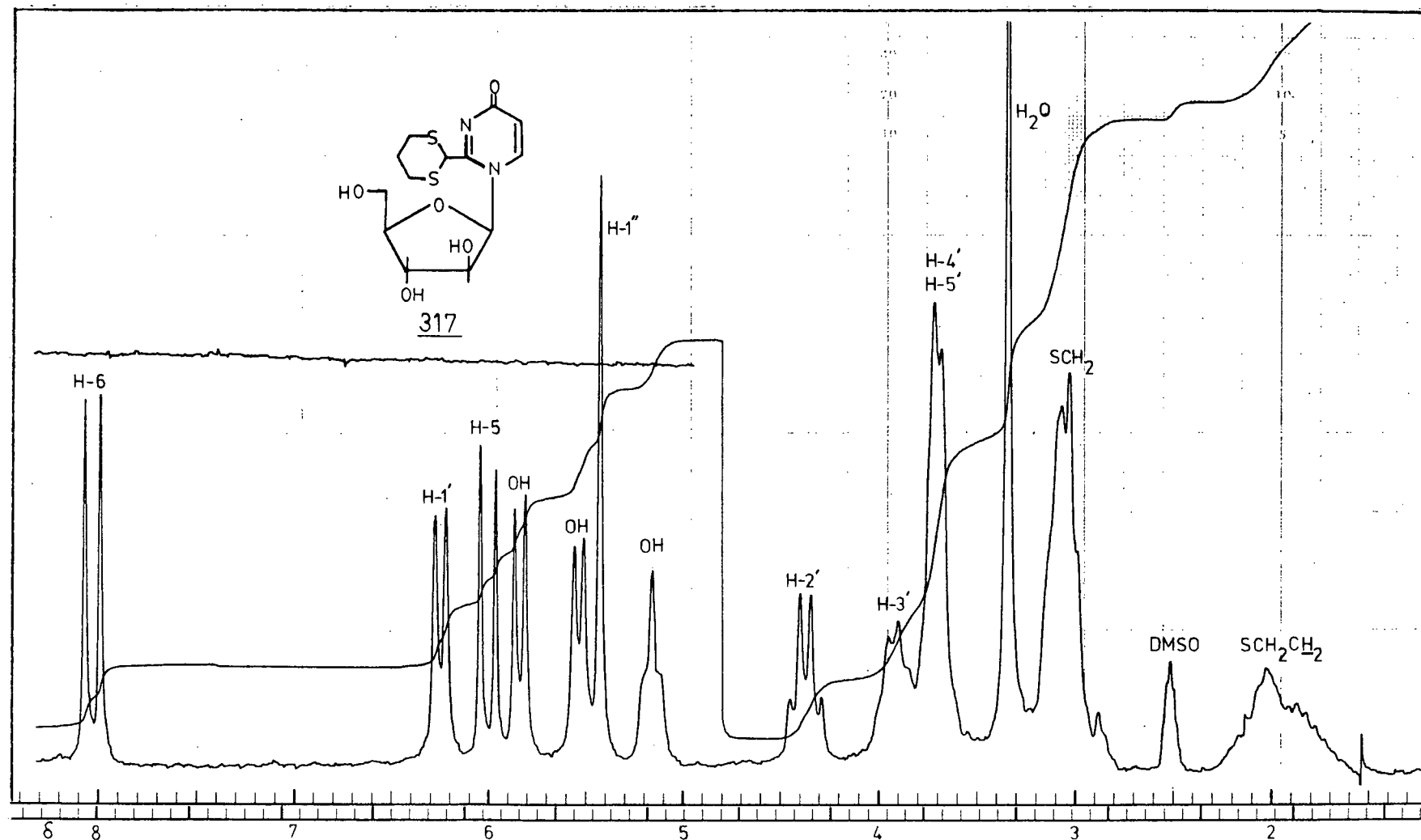
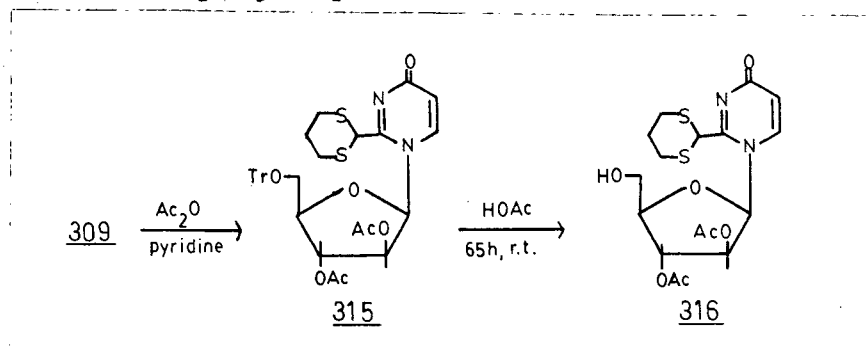


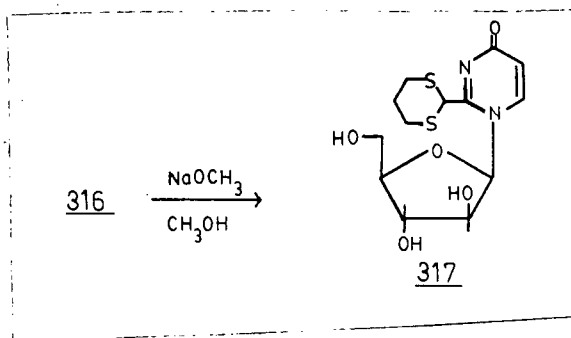
Figure IX. Partial 100 MHz PMR Spectrum of 2-(1,3-Dithian-2-yl)-1-β-D-arabinofuranosyl-4(1H)-pyrimidinone (317) in DMSO-d₆.

glycosidic C-N bond. Use of dilute mineral or acetic acid even at room temperature consistently resulted in aglycon cleavage. Because the presence of electron-withdrawing groups at C-2' and C-3' has been observed³⁷⁹ to decrease the ease of hydrolysis of the glycosidic linkage in nucleosides, compound 309 was acetylated in acetic anhydride-pyridine to give the 2',3'-di-O-acetyl-5'-O-trityl derivative 315. Having verified by n.m.r. spectroscopy that 315 was the appropriate di-acetate, this compound, purified by chromatography on silica gel, was allowed to stir in 80% aqueous acetic acid for 65 hours at room temperature. The resulting nucleoside 316, also purified by chromatography on silica gel, was obtained in 45% yield, indicating that some glycosidic cleavage had occurred. The n.m.r. spectrum of 316 in dimethyl sulfoxide- d_6 , clearly showed the presence of a D_2O -exchangeable hydroxyl proton with no evidence of the trityl group.



The acetate blocking groups of 316 were then easily removed by treatment of this compound with methanolic sodium methoxide to give the completely deprotected nucleoside 317. The n.m.r. spectrum of 317 in $DMSO-d_6$ (Figure IX) verified that this was the free nucleoside; the C-2' and C-3' hydroxyl groups gave rise to clearly resolved doublets at δ 5.52 and 5.83 while the primary hydroxyl group at C-5' appeared as a triplet (δ 5.15).

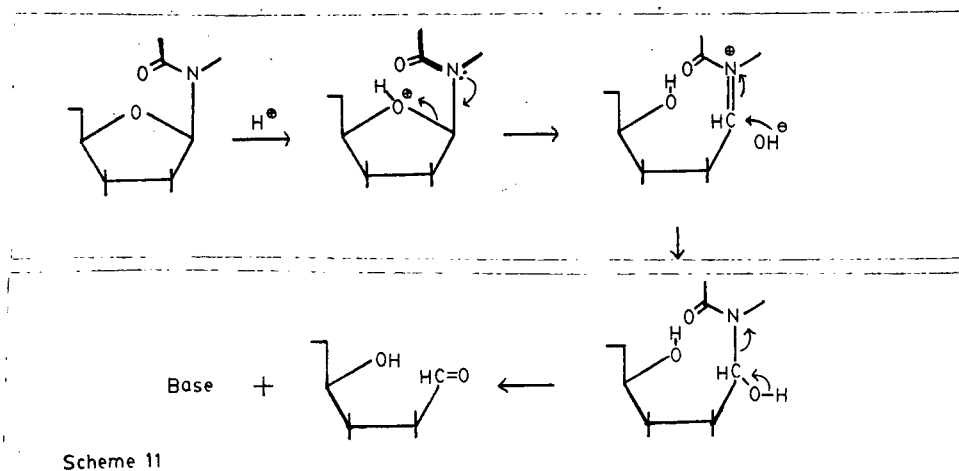
These three signals disappeared upon the addition of D_2O to the n.m.r. sample. The high resolution mass spectrum of 317 showed the appropriate molecular ion peak at m/e 347.0741.



3.1.7. Attempted Hydrolysis of the Dithioacetal of 315.

All attempts to hydrolyze the dithioacetal group of 315 to give the corresponding 2-formyl compound resulted in cleavage of the sensitive glycosidic bond. The methods employed were hydrolysis using mercuric chloride-mercuric oxide,¹⁹⁴ alkylative hydrolysis with methyl iodide-barium carbonate²³¹ and use of benzeneseleninic anhydride²³⁵.

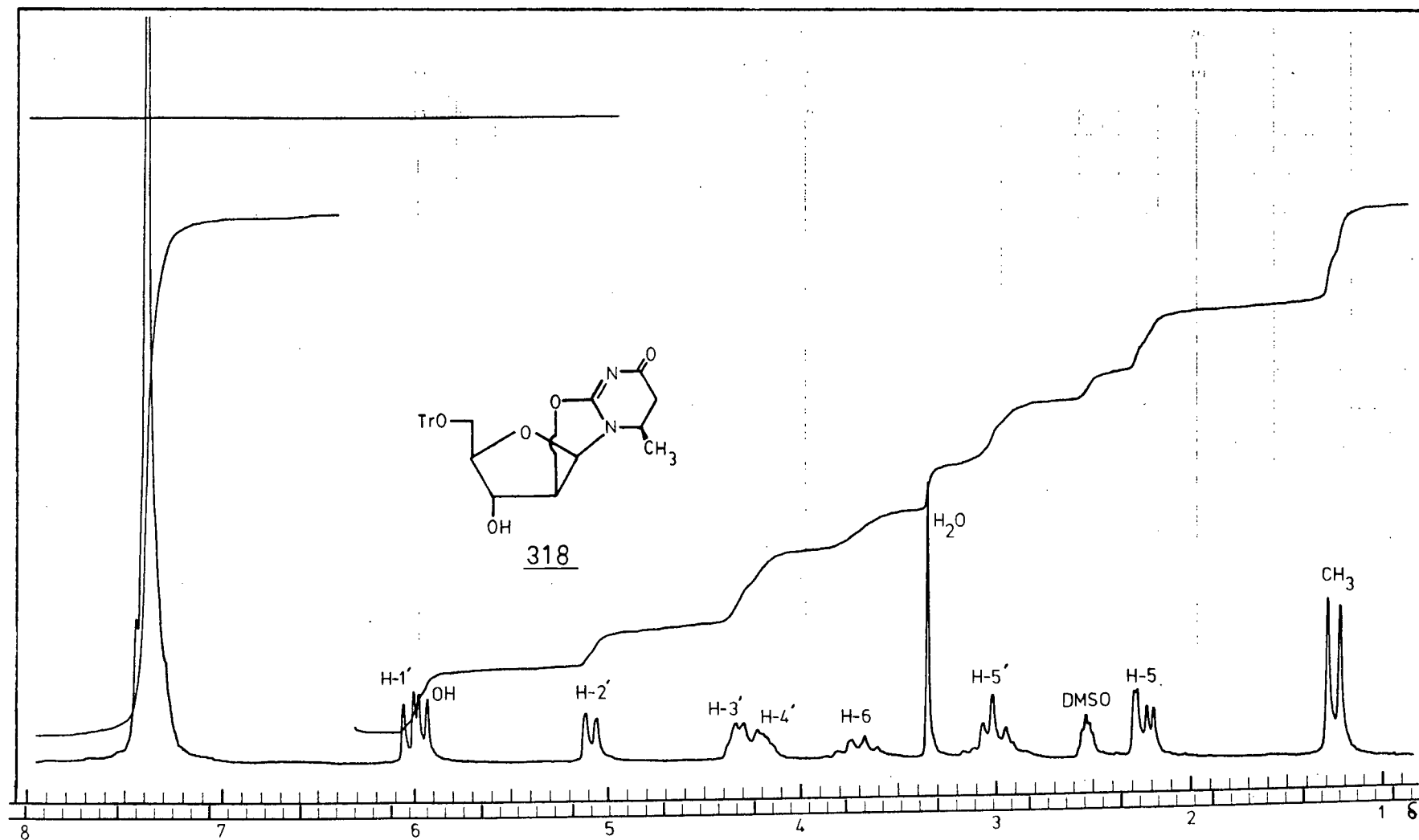
The reason for the lability of the glycosidic bond of these C-2 substituted pyrimidine nucleosides is unclear. The mechanism of the acidic hydrolysis of nucleosides is generally accepted³⁸⁰⁻³⁸¹ to involve initial protonation of the sugar-ring oxygen followed by formation of an unstable Schiff base (Scheme 11). Attack of the latter by water then leads to rupture of the N-glycosidic bond. Thus, any substituent which decreases the ease of protonation of the ring oxygen increases the stability of the glycosidic linkage³⁸². For instance, the presence of an electron-withdrawing substituent at C-2', such as an acetate group, instead of a hydroxyl group makes the electrons of the



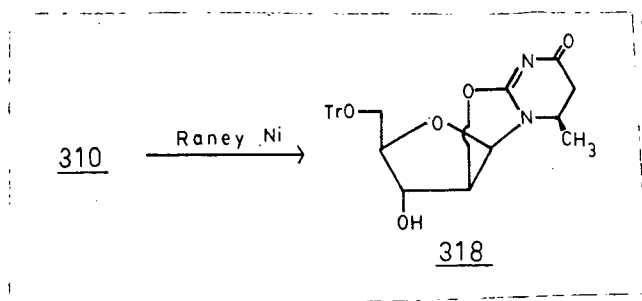
ring-oxygen less available for protonation with the result that the glycosidic bond is stabilized. This was shown to be true in the case of compound 315. Alternatively, any substituent on the base or the sugar moiety of the nucleoside which increases the susceptibility of the ring-oxygen to protonation also increases the acid-lability of the compound. The dithiane group of 309 obviously facilitates the protonation step, the sulfur atoms of the group perhaps aiding in the transfer of protons.

3.1.8. Desulfurization of 310 to Give 2,2'-Anhydro-5,6-dihydro-6-R-methyl-5'-O-trityluridine (318).

As mentioned above (Section 3.1.3.), the n.m.r. signals of the pyrimidine ring of the dihydro-anhydro nucleoside 310 were largely obscured by the high-field resonances of the dithianyl protons. In order to obtain clearer n.m.r. evidence of the presence of two C-5 protons, compound 310 was desulfurized with Raney nickel in ethanol to give the 6-methyl derivative 318. The n.m.r. spectrum of 318, taken in dimethyl sulfoxide- d_6 (Figure X), displayed a three-proton doublet at δ 1.27 having a coupling constant (J_{6,CH_3}) of 6.0 Hz. This signal was attributed to the



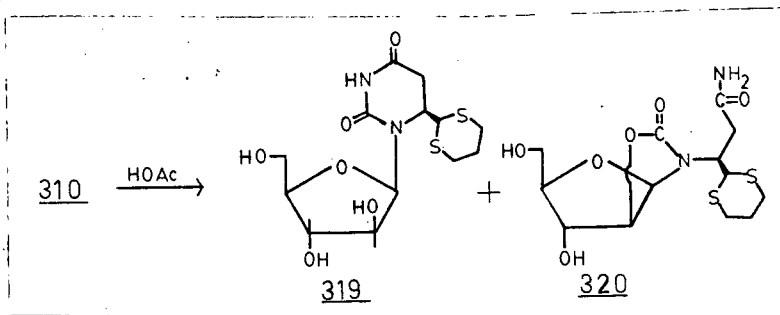
methyl group while H-5 appeared as a two-proton pair of doublets centred at δ 2.26 and H-6 as a one-proton multiplet at δ 3.70. These assignments were verified by irradiating the latter signal



(H-6); both doublets (H-5, CH_3) collapsed to singlets as required. Thus, the position of the dithianyl group at C-6 of 310 was firmly established.

3.1.9. 5,6-Dihydro-6-(S)-(1,3-dithian-2-yl)-1- β -D-arabinofuranosyluracil (319) and 3-[(S)-1-(1,3-dithian-2-yl)]propionamido- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (320).

When, in an attempt at detritylation, compound 310 was refluxed in 80% aqueous acetic acid for 10 minutes, two compounds, 319 and 320, were unexpectedly produced. These products were separated chromatographically on a weakly acidic cationic exchange resin.



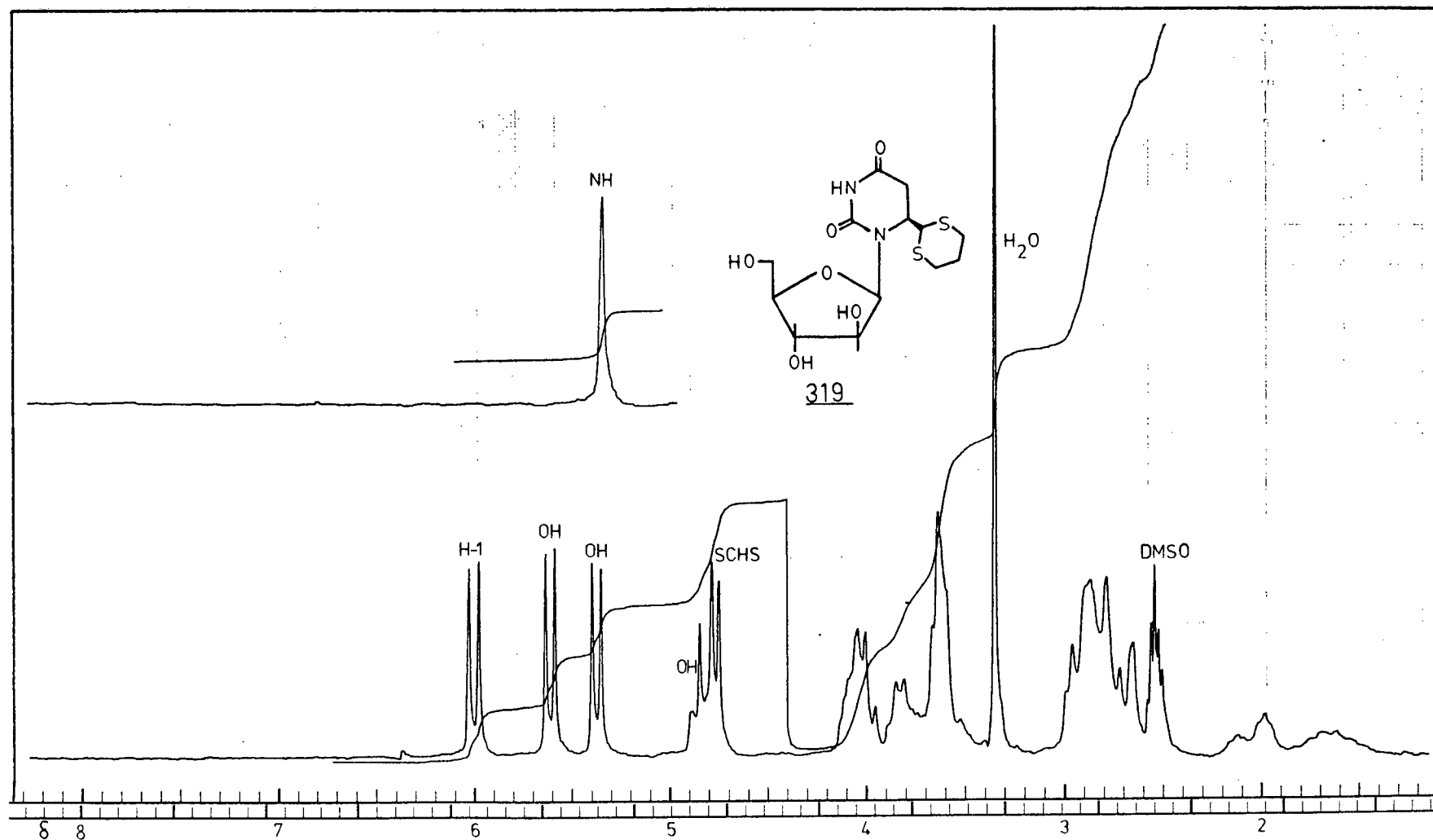


Figure XI. Partial 100 MHz PMR Spectrum of 5,6-Dihydro-6-(S)-(1,3-dithian-2-yl)-1-β-D-arabinofuranosyluracil (319) in DMSO-d₆.

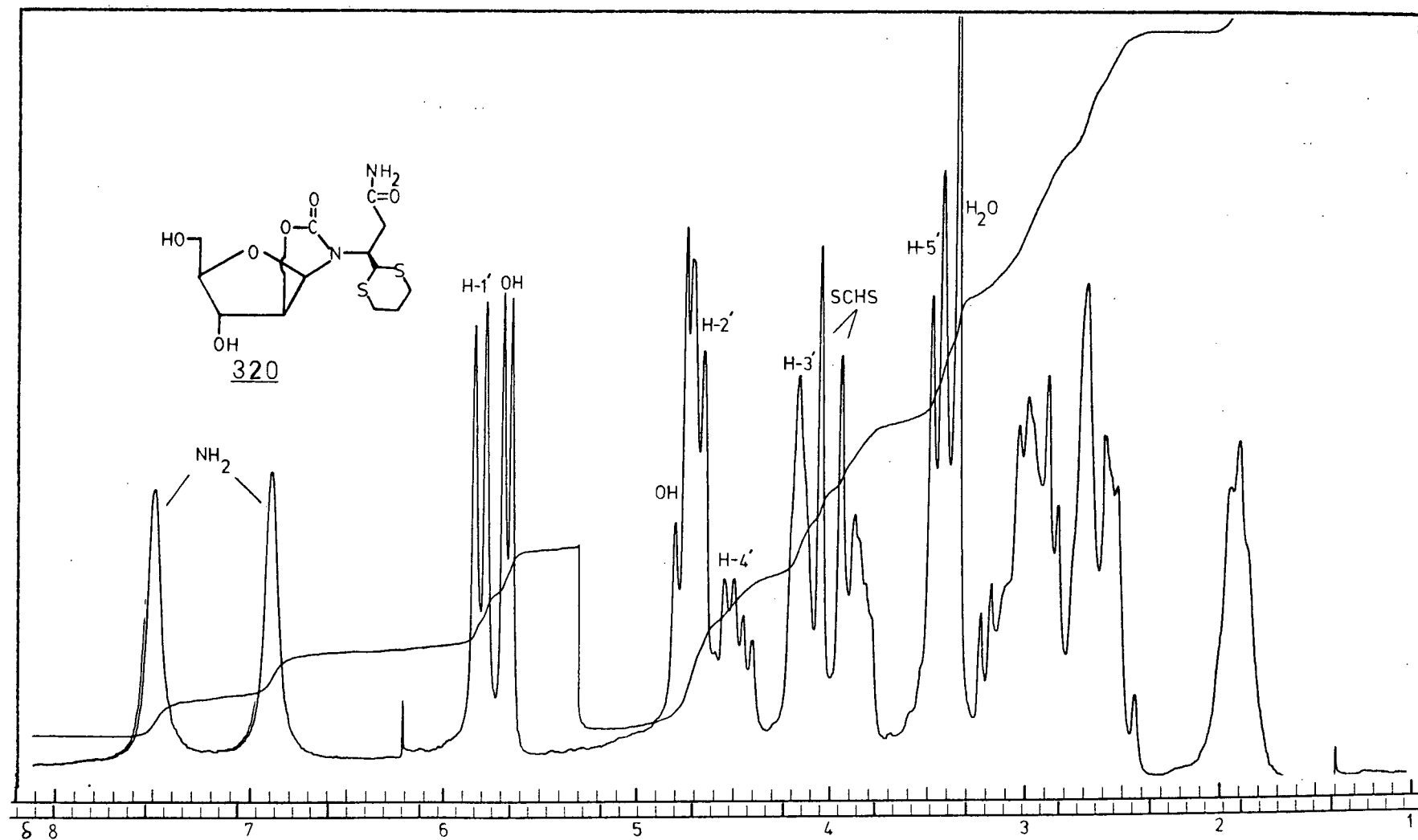
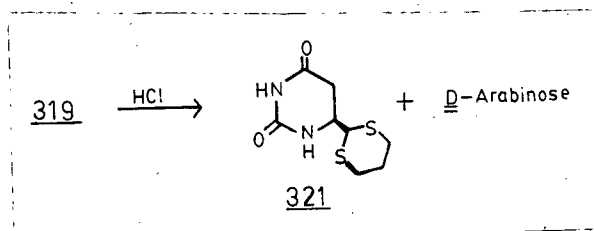


Figure XII. Partial 100 MHz PMR Spectrum of 3-[(S)-1-(1,3-Dithian-2-yl)]propionamido-β-D-arabinofurano-[1',2':4,5]-2-oxazolidone (320) in DMSO-d₆.

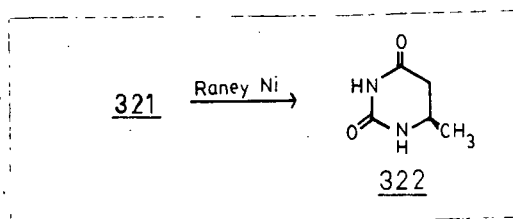
The faster-running component, compound 319, obtained in 5% yield after crystallization from aqueous methanol, was shown to be 5,6-dihydro-6-(S)-(1,3-dithian-2-yl)-1- β -D-arabinofuranosyluracil, that is, the compound arising from detritylation and hydrolysis of the 2,2'-anhydro linkage of 310. Acidic hydrolysis of 2,2'-anhydronucleosides to give nucleosides with the arabino configuration is well known.³⁸³

That compound 319 did not possess an anhydro structure was shown by the presence in its n.m.r spectrum (DMSO- d_6 , Figure XI) of one primary hydroxyl proton at δ 4.85 and two secondary hydroxyl protons at δ 5.60 and 5.36 as well as a low-field (δ 10.31), D_2O -exchangeable NH signal. The u.v. spectrum of 319 in methanol showed a maximum at 245 nm, the position of absorption of the dithiane ring,³⁸⁴ but no peaks above this value. The i.r. spectrum of 319 no longer displayed the characteristic anhydro-dihydro pattern seen in the precursor 310 but rather, closely resembled that of dihydrouridine,³⁸⁵ with peaks at 3400 (OH), 1710 (C=O), 1690 (C=O) and 1600 cm^{-1} (C=N of tautomer). Moreover, the mass spectrum of 319 displayed an intense peak at m/e 133 corresponding to the M^+ -base fragment. No typical anhydronucleoside fragmentation patterns were observed.³⁸⁶ Finally, the structure of 319 was confirmed by chemical means when it was treated with 1N hydrochloric acid for 4 hours at 60°. Hydrolysis of the glycosidic bond occurred under these conditions to yield D-arabinose, which was characterized by paper chromatography, and the corresponding free base 5,6-dihydro-6-(S)-(1,3-dithian-2-yl)uracil (321). The glycosidic bond of 5,6-dihydropyrimidine nucleosides has been observed to

be much more sensitive to acid hydrolysis than that of the corresponding unsaturated nucleosides.³⁸⁵



Compound 321 was in turn unambiguously characterized by its conversion with Raney nickel to the known 6-methyldihydrouracil (322).³⁸⁷



The structure of the second and major (90%) product formed by acid treatment of 310, that is, compound 320, was not so easily deduced by spectroscopic means as was 319 and recourse had to be made to chemical transformations of 320, to be discussed below (Sections 3.1.10-3.1.14), to achieve this end. Nevertheless, the i.r. spectrum of 320 discounted the possibility of a 2,2'-anhydro linkage in this compound; two carbonyl stretching peaks at 1680 (amide) and 1740 cm^{-1} (lactone) as well as a possible amide II peak at 1615 cm^{-1} were observed. The proton-decoupled ^{13}C -n.m.r. spectrum of 320 in D_2O corroborated the i.r. evidence of the presence of two carbonyl groups; two weak singlets at δ 177.0 and 159.8 were attributed to carbonyls of a primary amide and a carbamate group, respectively, based on correlations with the known ^{13}C resonances of these groups in other molecules.³⁸⁸ The ^1H -n.m.r. spectrum of 320 in dimethyl sulfoxide- d_6 (Figure XII)

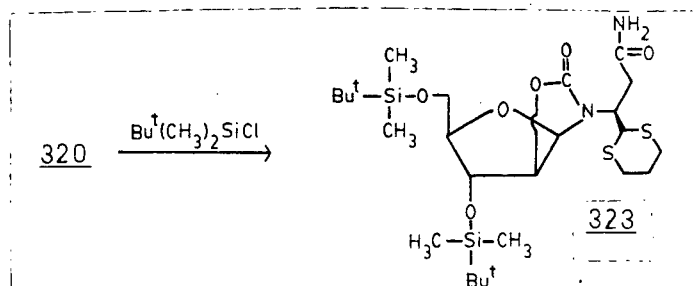
showed a primary hydroxyl proton as a triplet at δ 4.70 but only one secondary hydroxyl proton (δ 5.66), both of which exchanged rapidly with D_2O , together with two broad one-proton singlets at δ 6.86 and 7.51 which, however, exchanged slowly with D_2O . These two broad peaks were assigned to the two magnetically non-equivalent protons of a primary amide group based on the spectral data obtained for the following derivatives prepared from 320.

3.1.10. 3-[(S)-1-(1,3-Dithian-2-yl)]propionamido-3',5'-di-O-t-butyldimethylsilyl- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (323).

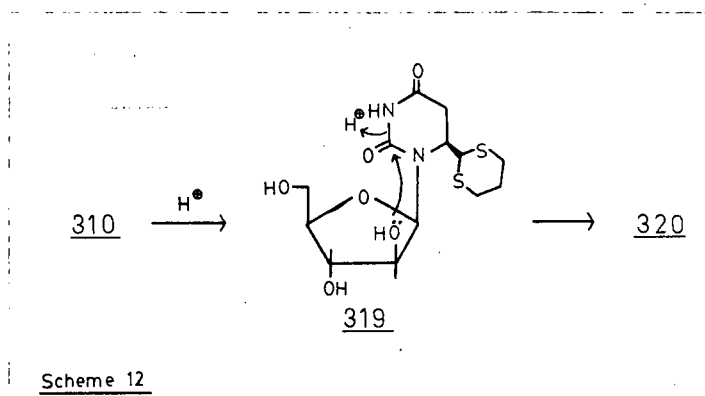
When compound 320 was treated with two equivalents of t-butyldimethylsilyl chloride in N,N-dimethylformamide-pyridine for 24 hours, the free hydroxyl groups were selectively silylated³⁸⁹ to give 323, the i.r. spectrum of which clearly revealed amide N-H stretching vibrations, previously buried by the intense hydroxyl absorptions in the spectrum of 320, at 3420 and 3230 cm^{-1} . These primary amide protons appeared in the n.m.r. spectrum of 323 as they had in that of the precursor 320, that is, as two broad, slowly exchangeable, low-field one-proton singlets.

3.1.11. 3-[(S)-1-(1,3-Dithian-2-yl)]cyanoethyl- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (328).

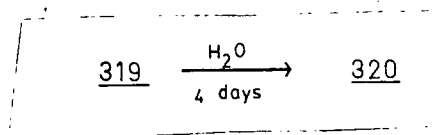
A possible mechanism to account for the formation of the



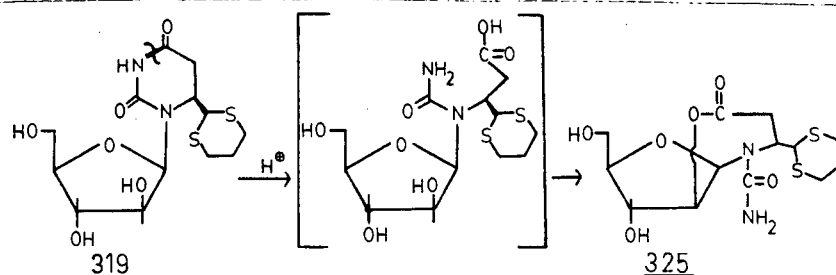
oxazolidone 320 from the tritylated anhydronucleoside 310 is depicted in Scheme 12. Initial acidic cleavage of the anhydro ring of 310, with concomitant detritylation, gives the arabinofuranosyluracil derivative 319 (which was isolated). Intramolecular attack at C-2 of the dihydropyrimidine ring of 319 by the appropriately disposed C-2' hydroxyl group then displaces the amide group and produces the 2-oxazolidone 320.



The intermediacy of 319 in the formation of 320 was easily demonstrated when a solution of 319 in water or alcohol was allowed to stand for 3-4 days. Quantitative conversion to the oxazolidone 320 occurred, as shown by n.m.r. spectroscopy and t.l.c. on silica gel.

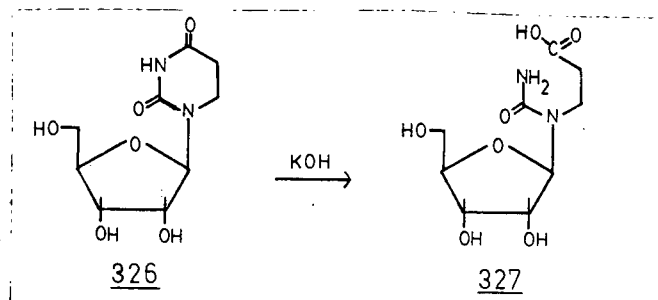


An alternate structure for 320 which would result from scission of the 3,4-bond of 319 with concomitant lactonization is 325 (Scheme 13). In fact, much evidence exists that this bond rather than the 2,3-bond of dihydropyrimidines³⁹⁰ and dihydropyrimidine nucleosides³⁸⁵ is cleaved under a variety of

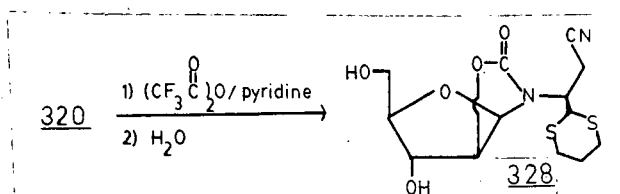


Scheme 13

conditions to give β -ureido acids. For instance,³⁹¹ treatment of 5,6-dihydrouridine (326) with potassium hydroxide causes complete conversion to the ureidopropionic acid 327. However,



the absence of a ureide group in compound 320 was demonstrated in the following two experiments. Firstly, 320 did not give a positive test with p-N,N-dimethylaminobenzaldehyde, a reagent known to react selectively with ureide derivatives of pyrimidines and pyrimidine nucleosides.³⁹² Secondly, treatment of 320 with trifluoroacetic anhydride-pyridine in anhydrous dioxane, conditions known to effect in high yield the dehydration of primary amides to the corresponding nitriles,³⁹³ followed by hydrolytic work-up of the reaction mixture gave compound 328 as a crystalline solid, the i.r. spectrum of which clearly showed a nitrile absorption at 2260 cm^{-1} as well as the single carbonyl absorption of the urethane structure at 1740 cm^{-1} . Though the possibility that a ureide functionality (as in 325) can also dehydrate to give the N-cyano derivative has not been dismissed, such cyano groups absorb in the i.r. in the 2000 cm^{-1} region.³⁹⁴

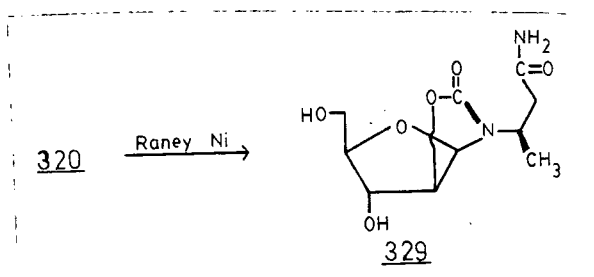


Thus, the tendency of the dihydropyrimidine ring of 319 to cleave as it does in acidic media is no doubt due to the presence of the cis C-2' hydroxyl group which can participate in the scission of the nearby 2,3-pyrimidine bond (Scheme 12) but not of the more distant 3,4-bond. The necessity of this cis relation between the hydroxyl group and the pyrimidine ring to effect 2,3-opening of the latter will be shown by the behaviour of the ribo analogue of 319 under acidic conditions, described below (see Section 3.2.4.).

3.1.12.

3-(R)-1-Methylpropionamido-β-D-arabinofurano-[1',2':4,5]-2-oxazolidone
(329)

In order to simplify the n.m.r. spectrum of the dithianyl oxazolidone 320, the latter was desulfurized with Raney nickel in water to give the non-fluorescent methyl derivative 329 as a syrup. The n.m.r. spectrum of 329 showed the expected doublet

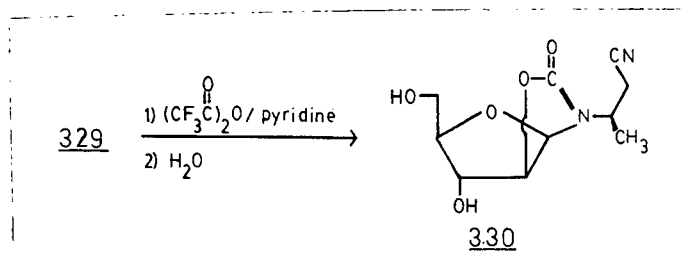


for the methyl group (δ 1.18) while the C-2 protons of the propionamide group appeared as a sharp doublet at δ 2.43 with a

coupling constant ($J_{1,2}$) of 7.0 Hz. The remaining signals of the spectrum were similar to those of the starting material 320.

3.1.13. Dehydration of 329 to Give 3-(R)-1-Methylcyanoethyl- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (330).

The primary amide group of 329, like that of 320, was dehydrated using trifluoroacetic anhydride-pyridine to yield the nitrile derivative 330. The i.r. spectrum of 330 showed the

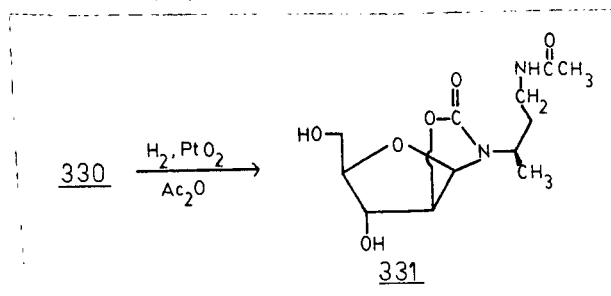


expected nitrile absorption at 2260 cm^{-1} and a carbonyl absorption at 1740 cm^{-1} while in the n.m.r. spectrum (DMSO-d_6), the two amide protons, seen at δ 6.80 and 7.44 in the spectrum of 329, were no longer visible. These results are completely consistent with those obtained in the analogous transformation of the dithianyl compound 320 to 328. In addition, the n.m.r. data showed a 0.49 ppm downfield shift of the C-2 proton resonance in going from the amide 329 to the more electronegative nitrile group of 330. This is possible only if C-2 and the nitrile group are adjacent so that 320 must have the primary amide structure rather than the alternative ureide structure (i.e. 325).

3.1.14. Hydrogenation of 330 to Give 3-(R)-1-

Methylacetamidopropyl- β -D-
arabinofurano-[1',2':4,5]-2-oxazolidone
(331).

Because the identification of the dithianyl compound 320 as the 2-oxazolidone rather than the ureide (325) hinged on its conversion to the nitrile (328), it was deemed essential to verify the presence of the nitrile functionality by chemical means as well as by the previously described physical methods and this could easily be done by catalytic hydrogenation of the nitrile to the amine. Moreover, having shown that the methyl derivative 330 displays chemical properties similar to its precursor 320, then the former compound was chosen for reduction studies because of its more easily interpreted n.m.r. spectrum. Thus, hydrogenation of 330 at 50 p.s.i. in acetic anhydride over platinum oxide for 24 hours gave 33% of the N-acetate 331, isolated by chromatography on silica gel (see Section 1.1.3. for a brief discussion of nitrile reductions). The i.r. spectrum of



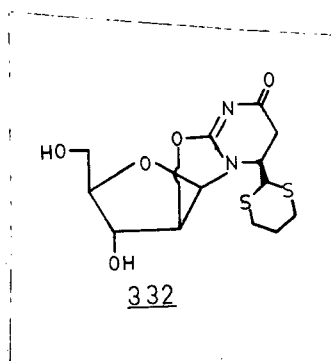
331 showed the appropriate carbonyl absorption of the N-acetate group at 1640 cm^{-1} as well as that of the 2-oxazolidone moiety at 1740 cm^{-1} . No nitrile peak could be seen. The n.m.r. spectrum of 331 in dimethyl sulfoxide- d_6 verified the presence of an acetamide group; a broad, one-proton singlet, which exchanged slowly with D_2O , was seen at $\delta 7.88$ while the acetate proton

signal appeared at δ 1.81 as a sharp singlet. The C-2 protons, now adjacent to the newly-formed C-3 methylene group instead of to the highly electronegative nitrile functionality, displayed an expected up-field shift to δ 1.72. The proton resonances of the arabinofuranose moiety of 331 were essentially identical to those of the starting material 330. Though chemical analysis of 331 showed the presence of 1.5 moles of water of hydration, a high resolution mass spectrum of the material substantiated the assigned formula of $C_{12}H_{20}N_2O_6$. Furthermore, a base peak in the mass spectrum at 114.0890 arising from the acetamidobutane fragment was further proof that the dihydrouracil ring of the anhydronucleoside 310 had cleaved at the 2,3-position during the acid-catalyzed detritylation step.

A considerable amount (36%) of higher R_f material was also obtained from the chromatography of the hydrogenation products of 330 and was identified by n.m.r. spectroscopy as a mixture of the 3'-O- and 5'-O-acetates of the acetamide 331. These two mono-O-acetates could not be separated by chromatography and no further attempts were made to purify these compounds. Formation of O-acetylated by-products was prevented by hydrogenating a solution of compound 330 in ethanol and acetic anhydride and by shortening the reaction period to 2 hours to give 331 as the sole product, thereby obviating the use of chromatography for purification.

3.1.15. Attempted Formation of 2,2'-Anhydro-5,6-dihydro-6-(S)-(1,3-dithian-2-yl)uridine (332).

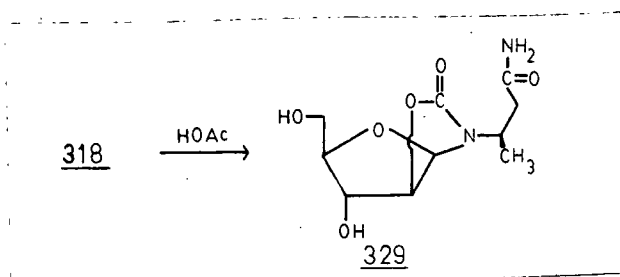
All attempts to detritylate the anhydrodihydronucleoside 310 to give the unblocked derivative 332 were unsuccessful. No



reaction was observed when, in an attempt to remove the trityl group by hydrogenolysis,³⁹⁵ compound 310 was held under 50 p.s.i. of hydrogen for 48 hours in the presence of palladium catalysts. Similarly, treatment of 310 with lithium in liquid ammonia resulted in recovery of starting material. Cleavage of the trityl group using either ferric chloride in methylene chloride³⁹⁷ or hydrogen chloride in anhydrous chloroform³⁹⁸ was partially successful; however, the detritylation was, in both cases, accompanied by a large amount of decomposition and side reactions, making these approaches unviable. A supposedly mild method³⁹⁹ of detritylation using trifluoroacetic acid followed by treatment with a basic ion-exchange resin resulted in simultaneous hydrolysis of the anhydro ring and dihydropyrimidine ring of 310 to give, as with acetic acid, the oxazolidone 320.

That the acid lability of the anhydro ring of 310 is a function of the position of attachment of the dithianyl moiety in the dihydro structure rather than of any assistance imparted

by the sulfur atoms of that moiety was shown by submitting the 6-methyl tritylated derivative 318, in which the sulfur atoms are absent, to the same hydrolytic conditions used on 310, that is, 10 minutes reflux in 80% aqueous acetic acid. Only compound 329 resulting from both anhydro and pyrimidine ring cleavage, was formed. This product was identical by n.m.r. spectroscopy and t.l.c. on silica gel to that obtained by Raney nickel desulfurization of 320.

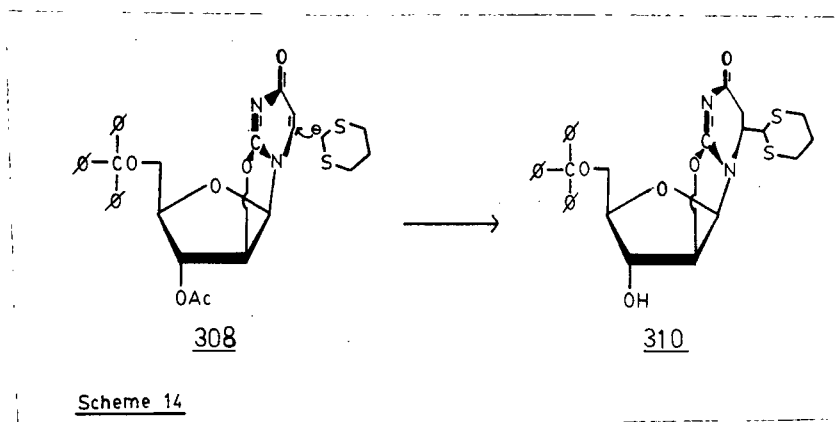


Curiously enough, none of the compound analogous to the arabino nucleoside 319, in which the dithianyl group is replaced by methyl, was isolated, indicating a possible inhibiting influence by the dithianyl group upon the hydrolysis of the dihydropyrimidine ring.

3.1.16. Assignment of the Configuration at C-6 of Compound 310 and its Derivatives.

Though the geometry at C-6 of 310 has not been unequivocally determined by direct correlation with a compound of known stereochemistry at this position, it would be expected that, as Paulsen²³⁶ has shown (see Introduction, Section 3.3.2.), the large dithianyl anion 126 would approach from the less sterically hindered side of a molecule. Since this corresponds to the exo side of the tritylated anhydronucleoside

308 (Scheme 14), then the 6-S isomer of 310 should result. No

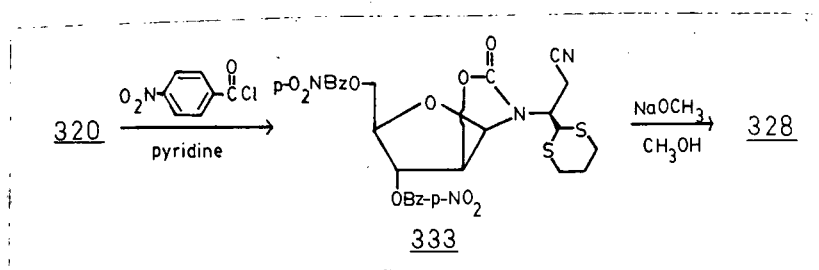


diastereomeric mixtures of compound 310 or its derivatives 318-320, 323, 328-331 could be detected by n.m.r. spectroscopy or chromatography. The 6-dithianyl arabinonucleoside 319 had a strong positive c.d. spectrum with a maximum at 250 nm which corresponds to the position of absorption of the dithianyl group.³⁸⁴ This suggests that compound 319 and by inference its precursor 310, are single isomers. As added proof that only one isomer about C-6 was formed in the reaction of 308 and 126, it was found that the free base, 5,6-dihydro-6-dithianyluracil (321) in which the only chiral centre is at C-6, exhibited a specific rotation of +22.7° in methanol.

3.1.17. 3-[(S)-1-(1,3-Dithian-2-yl)]cyanoethyl-3',5'-di-O-p-nitrobenzoyl-β-D-arabinofurano-[1',2':4,5]-2-oxazolidone (333) and 3-[(R)-1-Methylcyanoethyl-3',5'-di-O-p-nitrobenzoyl-β-D-arabinofurano-[1',2':4,5]-2-oxazolidone (334).

Before attempting hydrolysis of the dithioacetal of 320

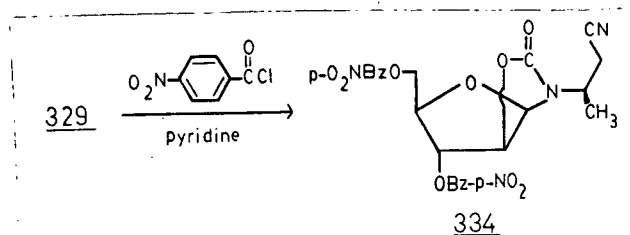
(described in the next section), it was thought desirable to block the free hydroxyl groups at the 3'- and 5'- positions, as well as the primary amide group in order to prevent complicating side-reactions. The p-nitrobenzoate group was considered suitable for this because of the crystallinity of the derivatives and its ease of removal under mildly basic conditions. However, when 320 was treated with excess p-nitrobenzoyl chloride in pyridine at room temperature, a single crystalline product was formed (333) whose n.m.r. spectrum showed the presence of only two benzoate groups instead of the expected three. No D₂O-exchangeable protons were observed. The i.r. spectrum of 333 revealed that, just as in the case of the treatment of 320 with trifluoroacetic anhydride and pyridine, dehydration of the primary amide to give the nitrile derivative had occurred. The characterization of 333 was verified by



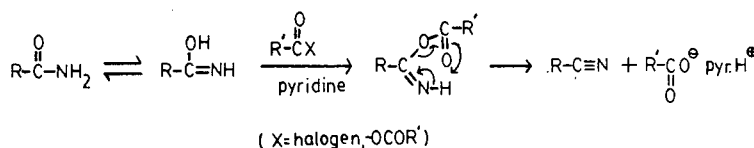
removal of its p-nitrobenzoyl groups with methanolic sodium methoxide, generating 328, identical in all respects with the compound obtained directly from 320 via the trifluoroacetic anhydride route.

Similarly, when the methyl derivative 329 was p-nitrobenzoylated, the blocked analogue of the nitrile compound 330 was obtained (334), as was evidenced by i.r. and n.m.r. spectroscopy.

Such dehydrations of primary amides to the corresponding

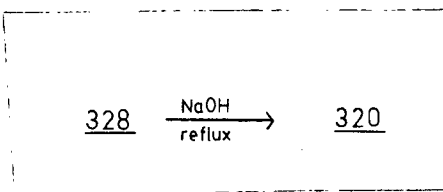


cyano compounds using anhydrides or acyl halides in pyridine have been well documented.⁴⁰⁰ The mechanism is thought³⁹³ to involve initial tautomerization of the amide to the hydroxy imine (Scheme 15), the hydroxyl group of which is subsequently acylated. Pyridine-catalyzed expulsion of the acyl group, facilitated by the presence of electron-withdrawing substituents on the latter, then gives the nitrile compound.



Scheme 15

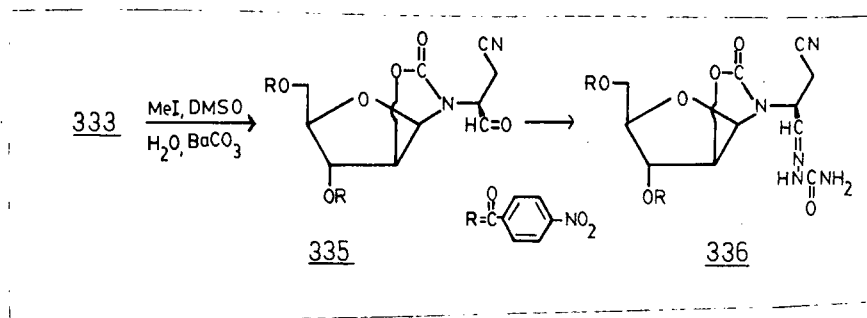
When compound 328 was refluxed for 1 hour in 1N sodium hydroxide solution, complete hydrolysis of the nitrile group to the primary amide occurred, thereby regenerating 320. This compound was characterized by comparison of its spectral data with that previously obtained for this compound.



3.1.18. Hydrolysis of the Dithioacetal of 333 to Give 3-(S)-1-Formylcyanoethyl-3',5'-di-O-p-nitrobenzoyl-β-D-arabinofurano-[1',2':4,5]-2-oxazolidone (335), Characterized as the Semicarbazone 336.

The feasibility of converting the dithianyl group of 333 to the formyl functionality was studied next. Though compound 333 is a greatly altered version of the natural nucleosides, it was hoped that the pyrimidine ring of this compound could be regenerated under the right conditions (see Section 3.1.18.). Moreover, compound 333 would serve as a model system for the dithioacetal hydrolysis of related molecules, to be described later (see Section 3.2).

Quite unexpectedly, it was discovered that 333 was completely inert to traditional mercuric chloride-mercuric oxide¹⁹⁴ S-S acetal hydrolysis, complete recovery of starting material being possible (see Introduction, Section 3.2 for a brief discussion of the methods of hydrolysis). Other reagents such as copper (II) chloride,²¹⁶ N-bromosuccinimide²¹⁷ and ceric ammonium nitrate²²⁵ also gave no reaction or led to extensive decomposition of starting material. Finally, though it was found that refluxing a solution of 333 in aqueous acetone and methyl iodide²³¹ had no effect on the dithiane group, use of aqueous dimethyl sulfoxide instead of acetone as the solvent led to complete alkylative hydrolysis of 333 to the aldehyde (335) after 3 hours at 60°. The aldehyde 335, which showed a low-field



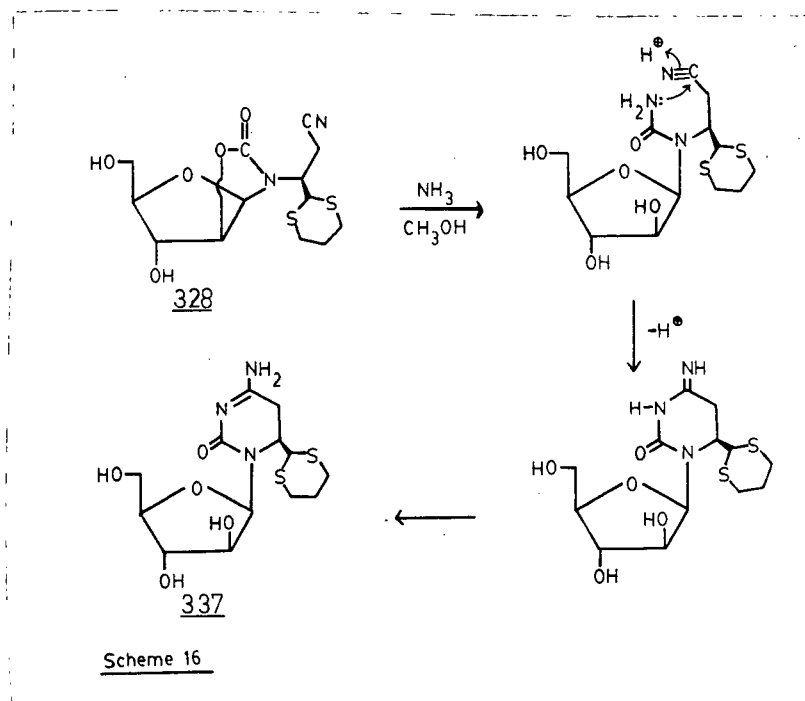
doublet (δ 9.45, DMSO- d_6) for the formyl proton, was converted to the semicarbazone 336 by treatment with semicarbazide

hydrochloride and pyridine in methanol. The crystalline derivative (336), which analyzed correctly, had an i.r. spectrum and an n.m.r. spectrum which were completely in accord with the proposed structure.

D. H. R. Barton has subsequently informed us that benzene-seleninic anhydride²³⁵ is an effective reagent for the conversion of 333 to the aldehyde 335.

3.1.19. Attempted Ring Closure of Compound 328.

It was at first expected that treatment of the cyano-2-oxazolidone 328 with methanolic ammonia would result in generation of the 5,6-dihydro-6-dithianylarabinocytosine derivative (337) by the mechanism outlined in Scheme 16.



However, when 328 was so treated with ammonia in a sealed bomb

at temperatures ranging from 20° to 160°, no reaction was observed even after 24 hours, as shown by complete recovery of starting material. This behaviour of 328 is not entirely surprising in view of the known stability of the 2-oxazolidone ring to acids and bases.⁴⁰¹

3.2. Reaction of 1,3-Dithiane Anion with Blocked 5-Bromouridine: Synthesis of a 6- β -Alanine Derivative of Uridine.

The synthesis of pyrimidine nucleosides substituted at C-6 with alkyl groups has been neglected for reasons discussed above (see Introduction, Section 6.) despite the knowledge that the C-5 substituted analogues often display potent chemotherapeutic properties.²⁹⁸⁻³⁰³ The foregoing results of the reaction of 1,3-dithiane anion (126) with the 2,2'-anhydronucleoside 308 suggested to us a novel and efficient method of introducing C-C bonded substituents at the 6-position of pyrimidine nucleosides by virtue of a) the propensity of the dithiane anion to add in a 1,4-fashion to the α,β -unsaturated carbonyl system of the pyrimidine ring, and b) the ability of the dithiane group to be easily converted to the versatile formyl group,¹⁹² thereby permitting further modification of the C-6 position.

The dithianyl-modified nucleoside analogues prepared above, though interesting in themselves particularly³⁰¹ in view of the arabino derivatives which resulted, were not conveniently amenable to further manipulation. The C-2 substituted nucleoside 309 displayed an extremely acid-labile glycosidic linkage while the anhydrodihydro nucleoside 310 could not be detritylated

without causing simultaneous rupture of the pyrimidine ring (to give 320) which, in turn, resisted attempts at re-cyclization (see Section 3.1.19.). The interesting 5,6-dihydro-6-dithianylarabinouracil derivative 319, available only in low yield by the procedure described, also displayed a tendency to pyrimidine-ring cleavage.

Thus, prompted by the report of Ueda and Inoue³²⁰ in which was described the addition of cyanide ion to C-6 of 5-bromouridine (see Introduction, Section 6.2.2.2.), the reaction of the latter nucleoside with the dithiane anion 126 was studied in view of finding a practical method of synthesizing a 6-formyluridine derivative. The results of this study are described below.

3.2.1. 5-Bromo-2',3'-O-isopropylidene-5'-O-trityluridine (340).

Although Ueda,³²⁰ in his study of the reaction of potassium cyanide with 5-bromouridine, used a 5'-O-acetyl derivative of the latter compound (i.e., 255), it was decided that for our present needs, a base-labile blocking group should be avoided. Thus, the known 2',3'-O-isopropylidene derivative (339)⁴⁰² of 5-bromouridine (338)⁴⁰³ was first prepared by standard procedures using acetone, copper sulfate and concentrated sulfuric acid. Reaction of 339 with one equivalent of triphenylmethyl chloride in pyridine at 100° for 2 hours⁴⁰⁴ then gave the crystalline trityl derivative 340. Compound 340, which analyzed correctly for bromine, showed the appropriate molecular ion peak in its mass spectrum (m/e 606 for ^{81}Br) while the n.m.r. spectrum of

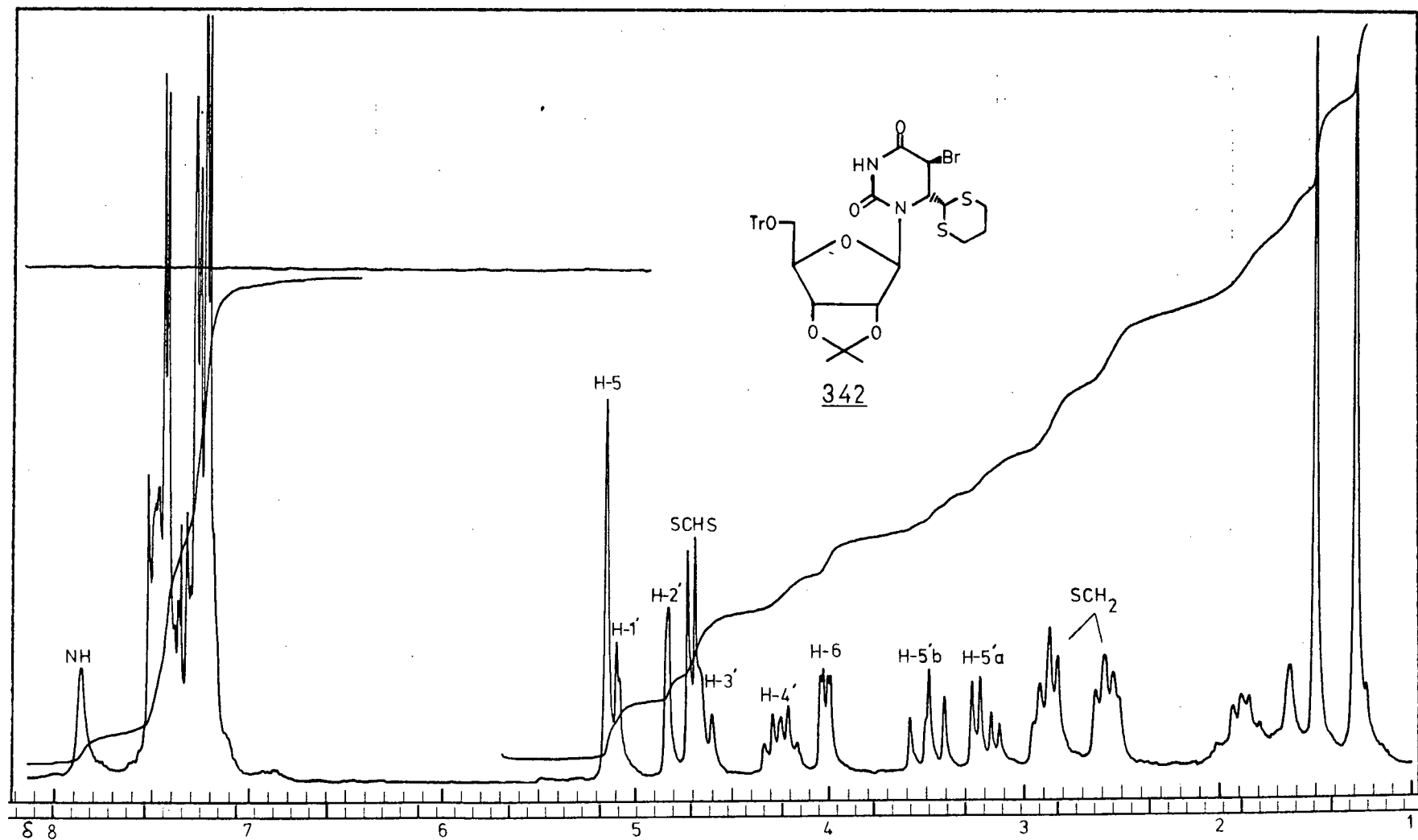
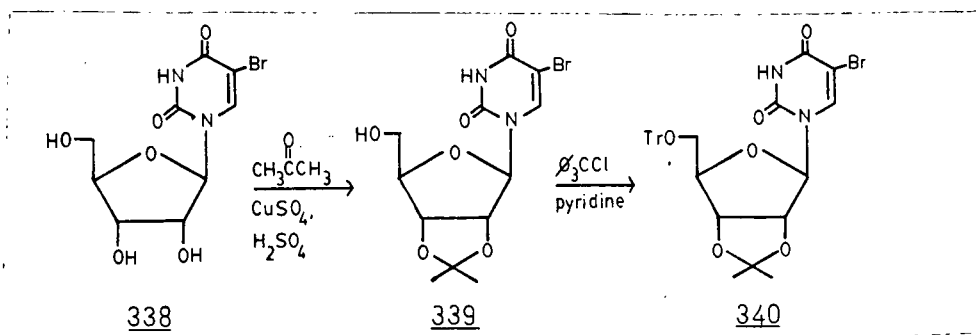


Figure XIII. Partial 100 MHz PMR Spectrum of 5-(S)-Bromo-5,6-dihydro-6-(S)-(1,3-dithian-2-yl)-2',3'-O-isopropylidene-5'-O-trityluridine (342) in CDCl_3 .



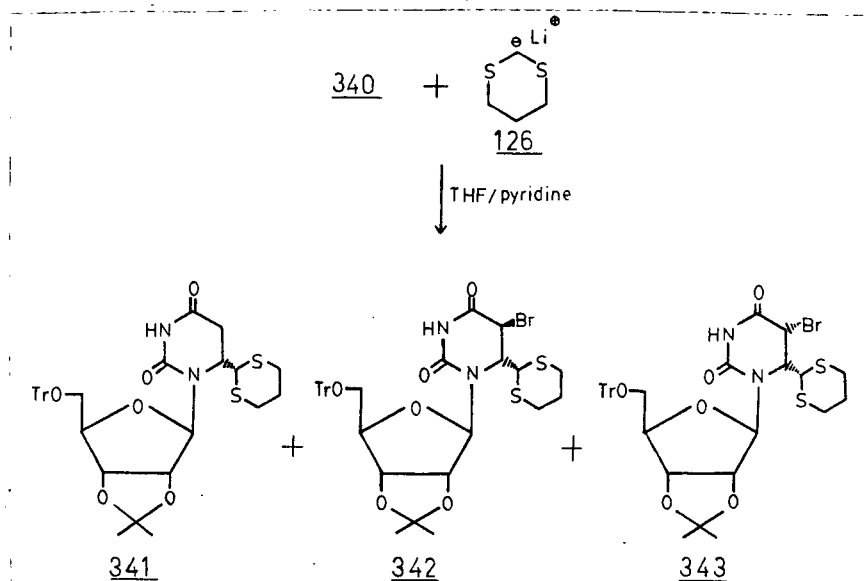
340, in addition to showing the isopropylidene and trityl group signals, displayed a singlet for H-6 at δ 7.86 (CDCl_3).

3.2.2. Synthesis of 5,6-Dihydro-6-(R)-(1,3-dithian-2-yl)-2',3'-O-isopropylidene-5'-O-trityluridine (341), 5-(S)- and 5-(R)-Bromo-5,6-dihydro-6-(S)-(1,3-dithian-2-yl)-2',3'-O-isopropylidene-5'-O-trityluridine (342 and 343).

Addition of a solution of the blocked 5-bromouridine 340 in anhydrous pyridine to a six-fold molar excess of 2-lithio-1,3-dithiane (126)¹⁹² in tetrahydrofuran at -78° under dry nitrogen gave, after a reaction period of 24 hours at -20° , the three dithiane addition products, 341, 342 and 343, isolated in yields of 37, 35, and 10%, respectively, by column chromatography on silica gel.

The identification of these three products by physical means will be discussed first, while their characterization by chemical transformations is reserved for subsequent sections.

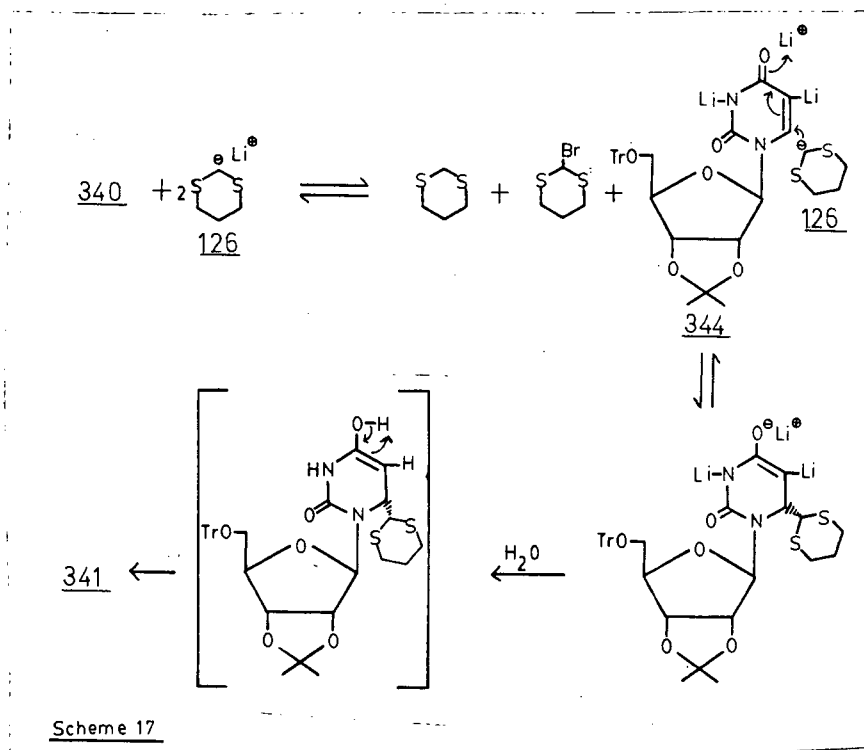
Neither the elemental analysis nor the mass spectrum of 341 showed presence of bromine, but simple nucleophilic displacement of the bromide of 340 by the dithiane anion was precluded by the



absence in the n.m.r. spectrum of 341, taken in deuteriochloroform, of a low-field singlet for H-6. Instead, a two-proton multiplet was seen at δ 2.48-2.71, suggesting a 5,6-dihydro structure.^{319 377} A similar n.m.r. spectrum was obtained for the 5,6-dihydro-6-dithianyl nucleoside 310.

The formation of compound 341 from the 5-bromouridine derivative 340 can be explained by assuming an initial vinyl halogen-metal exchange between 340 and the anion 126 to give the blocked 5-lithiouridine 344 (Scheme 17). It has been shown⁴⁰⁵ that in the presence of n-butyllithium, 5-bromouracil and its nucleosides exist in equilibrium with their 5-lithio derivatives. A 1,4-Michael-type addition at C-6 of another dithiane anion (which is in excess) would then give, after quenching, the 5,6-dihydro-6-dithianyl species 341. The proportion of 340 that is not consumed by the equilibrium reaction then goes on to give products 342 and 343 by a straightforward conjugate addition of the dithiane anion at C-6.

That compounds 342 and 343 bore a diastereomeric relationship was initially indicated by the behaviour of these compounds on silica gel. Whereas the reaction mixture of 340 and



126 had shown, by t.l.c. on silica gel, a preponderance of compound 343 with respect to 342, it was found that after chromatography of this same reaction mixture on silica gel, compound 342 was now the major product with respect to 343. Both 342 and 343 were shown to contain bromine by elemental analysis. However, though 342 analyzed properly for the formula $C_{35}H_{37}N_2O_6S_2Br$, the analysis of its isomer 343 did not show a complete mole of bromine, due, perhaps, to partial elimination of HBr during drying of the analytical sample in vacuo at elevated temperature. The chemical formula of 343 was thus confirmed by its high resolution mass spectrum which showed an M^+-CH_3 peak at 711.1027, corresponding to $C_{34}H_{34}N_2O_6S_2^{81}Br$. The peak arising from the ^{79}Br isotope was equally obvious.

A careful study of the n.m.r. spectra of 342 (Figure XIII) and 343 (Figure XIV), both taken in deuteriochloroform, permitted the assignment of the relative configurations of the bromine atom and the dithianyl group of these two compounds. For 342, H-

5 was seen as a doublet at δ 5.12 with a coupling constant ($J_{5,6}$) of 1.5 Hz, while for 343, H-5 was observed at slightly higher field (δ 4.80) but had a significantly larger $J_{5,6}$ value of 6.0 Hz. Now, since it has been shown by independent studies that 5,6-dihydrouracil (and its 5,6-substituted derivatives) exists mainly in a half-chair conformation⁴⁰⁶⁻⁴⁰⁹ (Figure XV) and furthermore, that cis hydrogens at these positions give rise to coupling constants ($J_{d,e}$) ranging from 5.2 to 7.23 Hz,⁴⁰⁹⁻⁴¹⁰ it was then inferred that 343 was the 5,6-cis isomer.

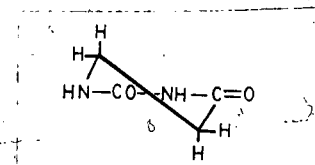


Figure XV. Half-Chair Conformation of Dihydropyrimidine Rings.

Compound 342 must therefore be the 5,6-trans isomer. This assignment is also consistent with the observed coupling constant ($J_{5,6} = J_{e,e} = 1.6$ Hz) of H-5 and H-6 in this compound since it can be assumed that the bulky bromo and dithiane substituents adopt the sterically favoured 5,6-diaxial relationship⁴⁰⁷⁻⁴⁰⁹ so that H-5 and H-6 are diequatorial (Figure XVI). Trans-diequatorial 5,6-hydrogens were observed to have

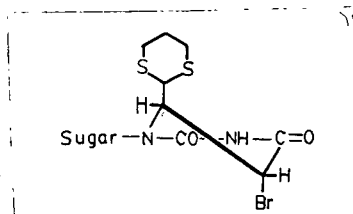
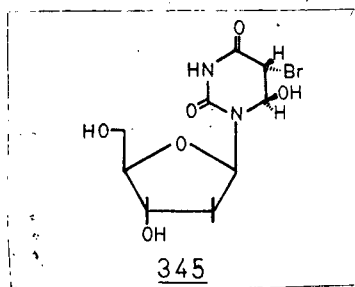


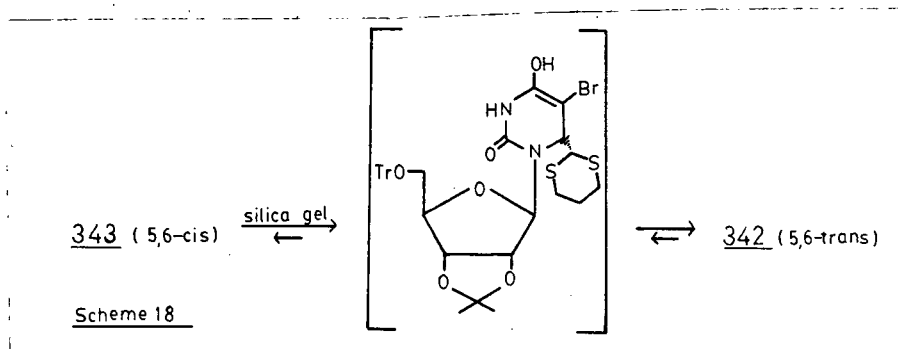
Figure XVI. The 5,6-Diaxial Relationship of the Dithianyl and Bromo Substituents of Compound 342.

$J_{5e,6e} = 2.5$ Hz in the n.m.r. spectrum of 5-bromo-2'-deoxy-5,6-dihydro-6-hydroxyuridine (345).⁴¹¹



The n.m.r. peak assignments of 342 and 343 were supported by decoupling experiments. The absolute configurations of these two compounds were determined by chemical means discussed later on (see Section 3.2.7.).

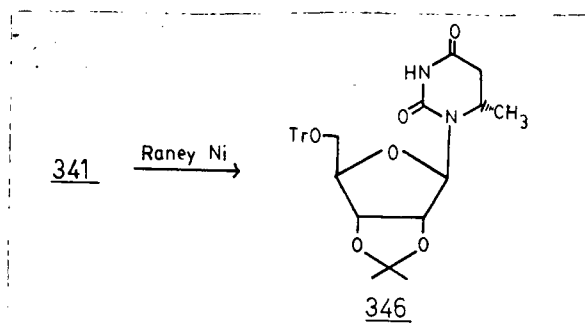
This stereochemical assignment of 342 and 343 as the trans and cis isomers, respectively is consistent with the observed instability of 343 on silica gel, in which this acidic medium catalyzes isomerization to the thermodynamically more stable 5,6-trans species (342), presumably via enolization of the C-4 carbonyl (Scheme 18).



It is interesting to note that, whereas the reaction of cyanide ion with 5-bromouridine gave a similar 1,4-Michael-type addition product which spontaneously dehydrobrominated to regenerate the 5,6-double bond,³²⁰ no such elimination was observed in this case of Michael-addition of 1,3-dithiane to give 342 and 343. This can be attributed to the much greater electronegativity of the cyanide group compared to the dithiane group with the resulting increase in the acidity of H-6 and consequent ease of elimination.

3.2.3. Desulfurization of 341 to Give 5,6-Dihydro-2',3'-O-isopropylidene-6-(S)-methyl-5'-O-trityluridine (346).

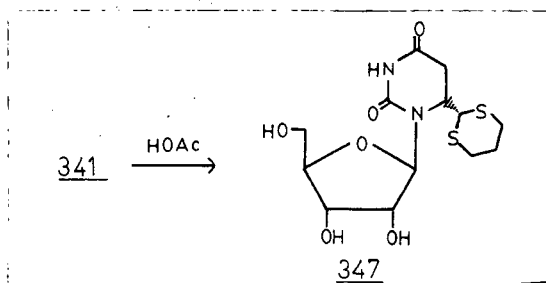
In order to simplify the high-field region of the n.m.r. spectrum of the 6-dithianyl nucleoside 341, the latter compound was desulfurized with Raney nickel in ethanol to give the 6-S-methyl derivative 346. The n.m.r. spectrum of 346 in deuteriochloroform showed the expected doublet for the C-6 methyl group at $\delta 1.36$. More importantly, H-5a, H-5e and H-6 gave rise



to an ABX pattern in the spectrum, the chemical shifts and coupling constants ($J_{5a,5b}$ 16.6 Hz) of which were again characteristic of a 6-substituted 5,6-dihydro system.^{319 377}

3.2.4. 5,6-Dihydro-6-(R)-(1,3-dithian-2-yl)uridine (347).

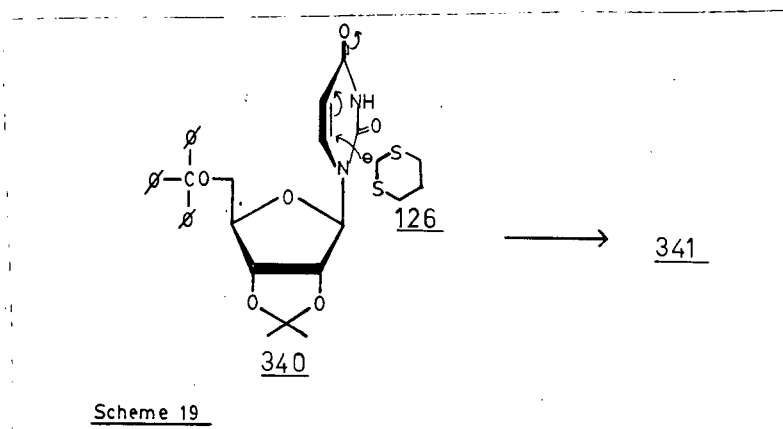
Treatment of the dihydronucleoside 341 with 80% aqueous acetic acid at refluxing temperatures yielded the completely unblocked compound 347. The n.m.r. spectrum of 347 (DMSO-d₆) showed the appropriate doublets for the secondary hydroxyls (δ 5.02 and 5.25) and triplet for the primary hydroxyl group (δ 4.84). The u.v. spectrum of 347 in methanol exhibited only a peak due to absorption by dithiane (245 nm); the fact that there was no absorption in the 260 nm region was a further indication



that the pyrimidine ring was saturated at the 5,6-position.³⁹⁰

There was no evidence that the ribo nucleoside 341 had undergone cleavage of the pyrimidine ring during the treatment with acetic acid. This is to be contrasted with the arabino analogue of 341 (i.e. compound 319) which displayed the anomalous tendency to cleave at the 2,3-position under mildly acidic conditions (see Section 3.1.9.). This behaviour of the pyrimidine ring of 319 can be related to the assistance provided by the nearby C-2' hydroxyl group, a situation not possible in the ribo nucleoside 347.

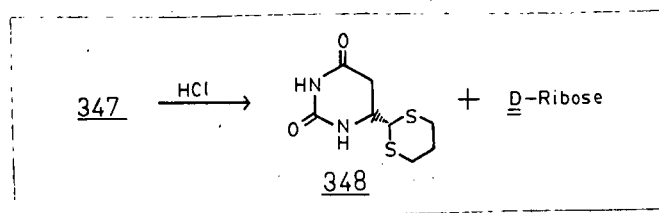
Compound 347 was assigned the 6-R configuration on the basis of its c.d. spectrum in methanol which showed a strongly negative Cotton effect with a maximum at 250nm ($\Delta\epsilon -4.13$). A positive Cotton effect at this wavelength was previously associated with the 5,6-dihydro-6-S-dithianyl nucleoside (319). The apparent stereoselectivity of the addition of 126 to the pyrimidine moiety of 340 (and its 5-lithio derivative 344) can be rationalized by assuming that these nucleosides adopt the more stable anti conformation in which, for steric reasons, the C-2 carbonyl group of the pyrimidine ring lies away from the plane of the sugar ring⁴¹²⁻⁴¹⁴ (Scheme 19). Endo attack by the dithiane anion (126) at C-6 is thus blocked by the bulky trityl group while exo attack, with formation of the 6-R isomer, is favoured. Such steric controls to the direction of addition of reagents at C-6 of pyrimidine nucleosides by the 5'-O-trityl



group have been observed.³³⁶

3.2.5. Hydrolysis of 347 to Give 5,6-Dihydro-6-(R)-(1,3-dithian-2-yl)uracil (348).

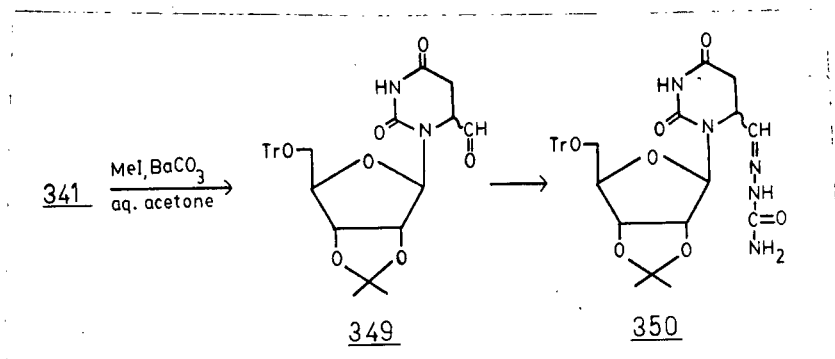
As a final chemical proof of structure of 341, its unblocked derivative 347 was hydrolyzed with 1M hydrochloric acid at 80° for 4 hours. White needles of the free dithianyl base 348 formed upon cooling of the reaction mixture. Recrystallization of 348 gave a compound identical by melting point and n.m.r. spectroscopy to 5,6-dihydro-6-(S)-(1,3-dithian-2-yl)uracil (321), previously obtained by similar treatment of the 6-S-arabino analogue 319. However, as expected from the result of the c.d. study of the intact molecule 347, compound 348 had an optical rotation of opposite sign to that of the 6-S isomer (321). Thus 348 and 321 are enantiomers.



3.2.6. 5,6-Dihydro-6-(R,S)-formyl-2',3'-O-isopropylidene-5'-O-trityluridine (349) and Its Semicarbazone 350.

Formation of the 5,6-dihydro-6-formyl nucleoside 349 by

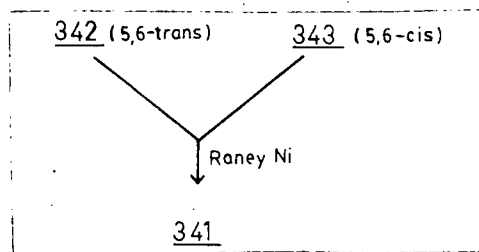
alkylative hydrolysis of the dithiane moiety of 341 using methyl iodide and barium carbonate in aqueous acetone proceeded smoothly at 55°. The 6-aldehyde 349 was characterized as its crystalline semicarbazone 350 by i.r. and n.m.r. spectroscopy and by chemical analysis.



The possibility of isomerization of the aldehyde group of 349 about C-6 owing to the acidity of the C-6 proton and the basic hydrolytic conditions employed has not been dismissed. This would perhaps explain the lack of resolution observed in the signals of the n.m.r. spectrum of the derived semicarbazone 350.

3.2.7. Debromination of Compounds 342 and 343 to Give 341.

Brief treatment of either the 5,6-trans compound 342 or its 5,6-cis diastereomer 343 with ethanolic Raney nickel⁴¹⁵ at refluxing temperatures gave the debrominated product 341, identical by R_f (silica gel), n.m.r. spectroscopy, mass spectrometry and, most importantly, optical rotation with that compound obtained directly from the reaction of 340 with the dithiane anion 126, the configuration of which was shown above to be R at C-6. Thus, compounds 342 and 343 must differ only in



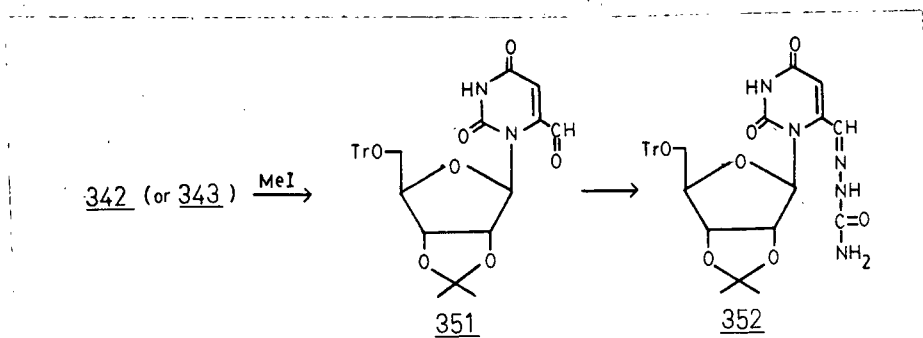
their configurations at C-5 so that 342, previously established as the trans isomer must have the 5S, 6S configuration while 343 must be the 5R, 6S isomer.

Although both 342 and 343 apparently underwent some desulfurization during the Raney nickel treatment, as shown by t.l.c. of the reaction mixture, these secondary products were not characterized.

3.2.8. 6-Formyl-2',3'-O-isopropylidene-5'-O-trityluridine (351) and 6-Formyl-2',3'-O-isopropylidene-3-methyl-5'-O-trityluridine (353), Characterized as Their Semicarbazones 352 and 354, Respectively.

It was felt, in view of Ueda's observation³²⁰ that 5-bromo-5,6-dihydro-6-cyanouridine spontaneously dehydrobrominates to give 6-cyanouridine, that hydrolysis of the dithioacetal of 342 (or 343) to the 6-aldehyde derivative would also result in concomitant elimination of HBr because of the increased acidity of the C-6 proton. In this way, the desired 5,6-double bond would be regenerated. To test this hypothesis then, the trans isomer 342 was treated with methyl iodide and barium carbonate in aqueous acetone containing 10% dimethyl sulfoxide. An n.m.r. spectrum of the crude worked-up reaction mixture showed,

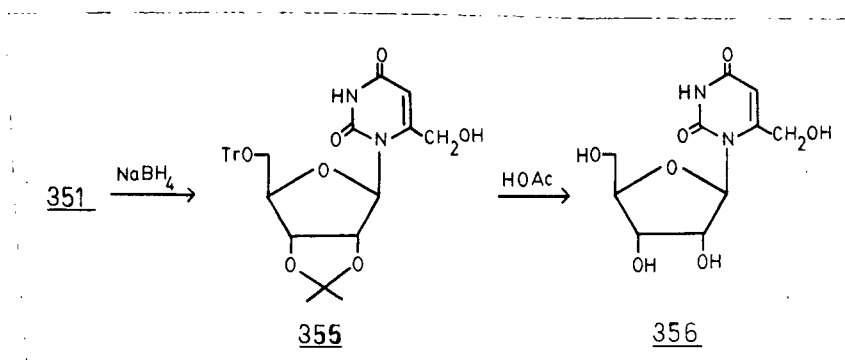
in deuteriochloroform, a singlet for the formyl proton at δ 9.53, the same position reported by Klein and Fox³¹⁸ for the formyl proton of 2',3',5'-tri-O-acetyl-6-formyluridine (242, R=CHO). Since the same authors also stated that the last-named compound was unstable, the aldehyde 351 was characterized as its semicarbazone 352. The n.m.r. spectrum of 352 in dimethyl



sulfoxide- d_6 displayed, in addition to four D_2O -exchangeable protons (NH), a singlet for H-5 at δ 5.96 (superimposed on H-1', also a singlet) as well as a sharp singlet at δ 7.57 attributed to the imine proton. This, in addition to the proper elemental analysis and mass spectrum of 352 was convincing proof that HBr had been eliminated from 342 to give 351 and thence 352.

A few points about the alkylative hydrolysis of 342 to the aldehyde 351 deserve mention. When the reaction was conducted in 10% aqueous acetone at 55°, only partial hydrolysis was observed by t.l.c. even after seven days of reaction. When 10% by volume of DMSO was included in the reaction mixture, complete thioacetal hydrolysis was accomplished within four days at 55°C. However, in addition to the 6-aldehyde 351, a minor, higher R_f compound was also formed. This compound was shown to be the N-3 methylated 6-aldehyde 353, also characterized as its semicarbazone, 354. The n.m.r. spectrum of 354 showed only three D_2O -exchangeable protons but now, a three-proton singlet due to

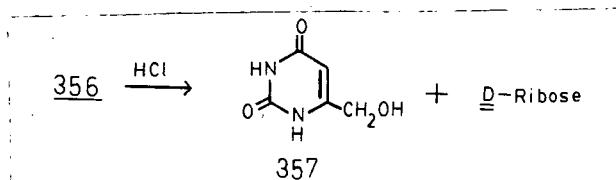
upon addition of D_2O , with a geminal coupling constant of 6.4 Hz. The i.r. spectrum of 355 in chloroform solution showed a sharp N-H absorption at 3420 cm^{-1} superimposed on a broad O-H band. When compound 355 was refluxed in 80% aqueous acetic acid for 25 minutes, 6-hydroxymethyluridine (356) was isolated as a clear syrup after purification by chromatography on Bio-Rex 70 cation exchange resin (H^+ form). The n.m.r. spectrum of 356 in dimethyl



sulfoxide- d_6 was completely consistent with the assigned structure, having a total of five D_2O -exchangeable protons. The C-6 methylene signal was observed as a broad singlet which sharpened after D_2O addition. The u.v. spectrum of 356 in methanol exhibited a maximum at 258 nm due to the unsaturated pyrimidine moiety.⁴¹⁷

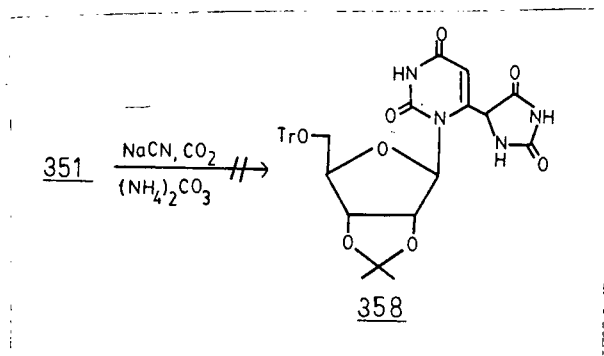
3.2.10. 6-Hydroxymethyluracil (357).

Although Ueda³³¹ has reported a melting point for 5'-O-acetyl-6-hydroxymethyl-2',3'-O-isopropylideneuridine, no other physical constants for 6-hydroxymethyluridine (356) or its derivatives are known. Accordingly, in order to confirm the structural assignments of 355 and 356, the latter compound was subjected to acid hydrolysis using 1M hydrochloric acid at 90° for 12 hours, yielding the known 6-hydroxymethyluracil 357.⁴¹⁸



3.2.11. Attempted Synthesis of 6-(2,4-diketotetrahydroimidazol-5-yl)-2',3'-O-isopropylidene-5'-O-trityluridine (358).

Since, as mentioned previously, our ultimate goal was to attach a C-C linked amino acid side-chain at C-6 of uridine, application of the Bucherer hydantoin synthesis¹⁴² to the aldehyde 351 was considered a convenient route to such a compound. This reaction was previously used to synthesize the 3-C-hydantoate 280 (see Section 1.2.3.) from which the 3-C-glycylallofuranose 281 was successfully formed. However, when the nucleoside 351 was submitted to the same conditions, that is, heating at 50° for 12 hours in methanol in the presence of sodium cyanide and ammonium carbonate under three atmospheres of carbon dioxide, t.l.c. of the reaction mixture showed that at least eight different compounds had formed in addition to decomposition products, the latter appearing as base-line material on the plate. No attempt was made to isolate any of these products. It thus appeared that the sensitive³¹⁸ 6-aldehyde 351 was not able to withstand the strongly basic conditions required for hydantoin synthesis.



3.2.12. E-(or Z)-6-[(2-Carboethoxy-2-cyanoethylidene)-2',3'-O-isopropylidene-5'-O-trityluridine (359) and E-(or Z)-6-[(2-carboethoxy-2-cyanoethylidene)-2',3'-O-isopropylidene-3-methyl-5'-O-trityluridine (360)].

Since application of the hydantoin synthesis to the 6-aldehyde 351 failed, it was decided to attempt synthesis of a C-6 β -amino acid derivative by the somewhat milder Knoevenagel condensation of ethyl cyanoacetate (263) with the 6-formyl nucleoside 351. The reactions of 263 with the 3-ketose 14 (Section 1.1.2.) and the 2,5-anhydro-D-allose 203 (Section 2.1.1.2.) were used as models for the present study.

Thus, because it was thought best not to attempt separation of the sensitive aldehydes, a solution of a mixture of 351 and 353, and ethyl cyanoacetate (263) in anhydrous N,N-dimethylformamide was stirred for 2 hours at room temperature in the presence of a catalytic amount of ammonium acetate as base. Two products, 359 and 360, were isolated by column chromatography on silica gel in yields of 38% and 10%, respectively. The n.m.r. spectra of both these compounds in deuteriochloroform were essentially identical, showing the ethyl ester signals as a clean triplet (CH_3) and quartet (CH_2) around δ 1.40 and 4.40, respectively, as well as a low-field (δ 8.1) singlet for the branched-chain vinyl proton. However, whereas 359 showed a broad, low-field, D_2O -exchangeable signal for the N-3 proton (Figure XVII), no such signal was seen in the spectrum of 360. Instead, a sharp 3-proton singlet at δ 3.14

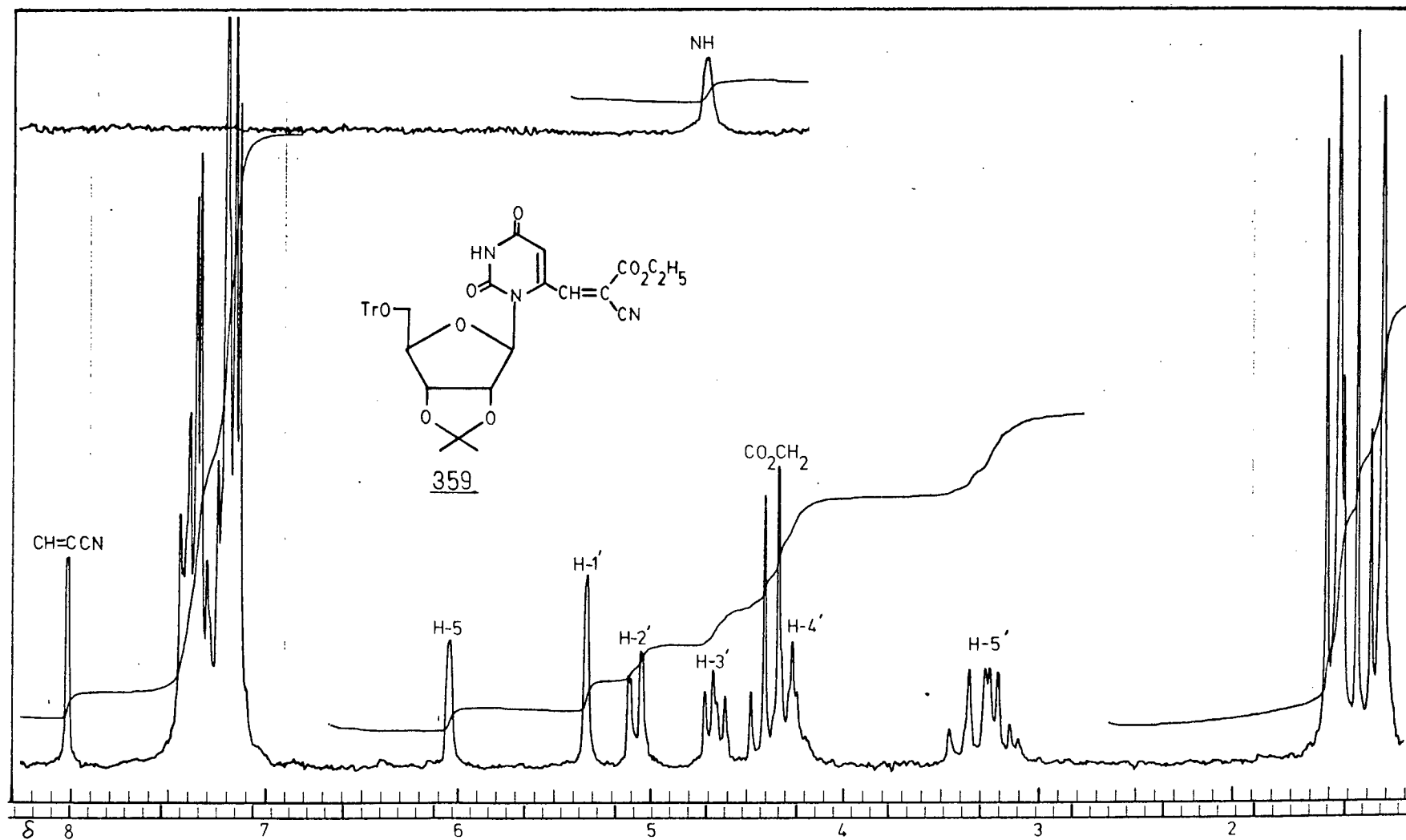
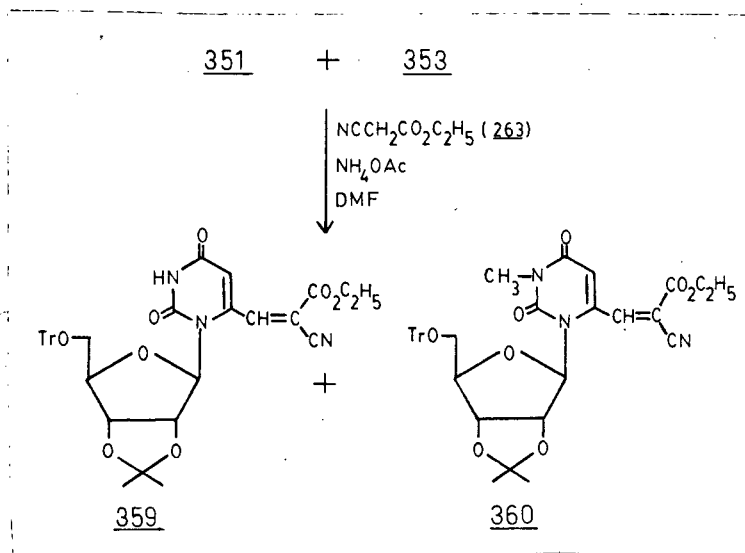


Figure XVII. Partial 100 MHz PMR Spectrum of E-(or Z)-6-[(2-Carboethoxy-2-cyano)ethylidene]-2',3'-O-isopropylidene-5'-O-trityluridine (359) in CDCl₃.

indicated that 360 was the N-3 methyl derivative. The



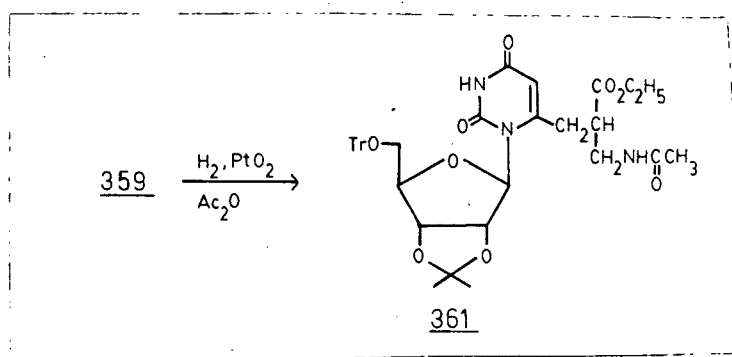
i.r. spectrum of 360 in carbon tetrachloride solution substantiated the absence of the N-H group and moreover, displayed three carbonyl signals at 1745, 1725, and 1680 cm⁻¹ which served as proof that 360 as well as the precursor 353 and its semicarbazone 354 were N-methylated rather than O-methylated.

The lack of multiplicity in the signals of the n.m.r. spectra of 359 (Figure XVII) and 360 was taken as evidence that only one of the possible E and Z isomers had been formed in each case. It has been demonstrated (see Introduction, Section 2.3.2.1.) that ethyl cyanoacetate (263) generally reacts with aldehydes in a stereoselective manner to give the geometrical isomer in which the two bulkiest groups are trans.¹⁸⁵⁻¹⁸⁶ Accordingly, in both compounds 359 and 360, the isomer in which the carboxyethyl and nucleoside moiety are trans would be preferred. No attempt was made to verify this tentative

assignment since the next step (hydrogenation) in the planned synthesis of uridinyl β -alanine was expected to destroy this center of geometrical isomerism.

3.2.13. Hydrogenation of 359 to Give 6-[(2-(R or S)-Carboethoxy-2-acetamidomethyl)ethyl]-2',3'-O-isopropylidene-5'-O-trityluridine (361).

No further work was done on the N-3 methyl derivative 360. Compound 359, however, was hydrogenated for 20 hours at 50 p.s.i. in acetic anhydride using platinum oxide as the catalyst to give the N-acetyl derivative 361. Though 361 analyzed

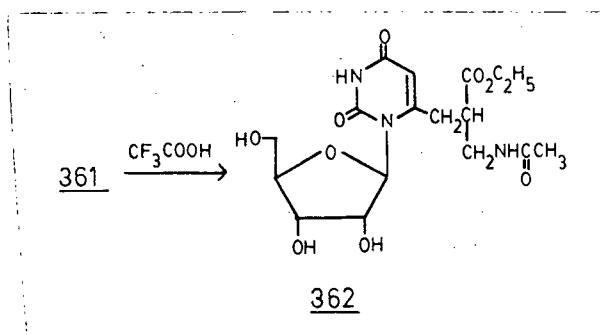


properly for $C_{39}H_{43}N_3O_9$, its mass spectrum showed, in addition to the molecular ion peak at m/e 697, several higher mass peaks centered at m/e 709, indicating that partial reduction of the trityl group had occurred. This was confirmed by the n.m.r. spectrum of 361 in deuteriochloroform which showed a very complex pattern of high field signals arising from the reduced phenyl rings. However, from this spectrum it could still be concluded that a) the exocyclic vinylic proton seen at δ 8.1 in the n.m.r. spectrum of the unreduced compound 359 was no longer present so that the exocyclic double-bond was now saturated, b) the nitrile group was converted to the N-acetamide as shown by

the appearance of an additional D_2O -exchangeable NH signal and a sharp singlet at δ 1.95 and c) the pyrimidine ring of 361 was not reduced since the C-5 proton was observed as a sharp singlet at δ 5.64. Selective reduction of unsaturated side-chains of pyrimidine nucleosides is not uncommon.²⁹⁷

3.2.14. 6-[3-Amino-2-(R or S)-carboxypropyl]uridine (363).

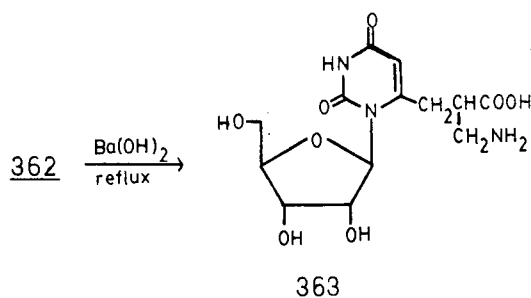
Treatment of the blocked nucleoside 361 with trifluoroacetic acid at room temperature gave the partially unblocked derivative 362. The n.m.r. spectrum of 362 in dimethyl sulfoxide- d_6 indicated that the isopropylidene and trityl groups of 361 had been removed, generating one primary and two secondary hydroxyl groups. The high-resolution mass spectrum of



362 did not show a molecular ion peak; instead, the highest mass fragment was that corresponding to the protonated base moiety (BH^+), a typical fragmentation pattern for N-glycosides.

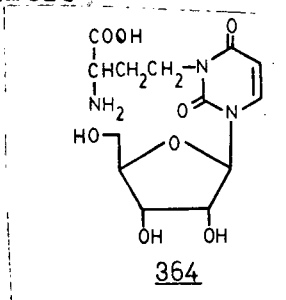
Removal of the base-labile blocking groups of the amino acid moiety of 362 was accomplished by refluxing a solution of the latter compound in concentrated aqueous barium hydroxide for 6 hours. The ninhydrin-positive material so obtained (363) was purified by chromatography on a weakly acidic cation (H^+)

exchange resin. While the n.m.r. spectrum of 363 in dimethyl sulfoxide- d_6 no longer showed the presence of either the N-acetate group or the ethyl ester group and the mass spectrum of 363 displayed the appropriate molecular ion peak (M^+H) at m/e 346, the chemical analysis of this substance indicated the presence of barium salts. When a strongly-acidic cation exchange resin (Dowex 50W-X2) was used to attempt removal of the barium ions from 363, the organic material recovered was no longer ninhydrin-positive.



The c.d. spectra of nucleosides 362 and 363 in water showed extremely weak negative Cotton effects in the 260 nm region. This is consistent with the observation that 6-substituted pyrimidine nucleosides in the β -configuration adopt the syn conformation⁴²⁸ (see Section 3.2.4).

The β -alanyl nucleoside 363 is a structural isomer of N^3 -(3-L-amino-3-carboxypropyl)uridine (364), found⁴²⁹ at position 47 in the extra loop of E. coli tRNA. Compound 364 has been synthesized by Seela and Cramer.⁴³⁰



IV BIOLOGICAL ASSAY

In in vivo tests, compounds 317 and 320 were found to be inactive against Leukemia 1210.⁴²⁶

Compounds 317, 319, 320, and 347 exhibited, respectively, 24, 13, 8 and 24% inhibition of L1210 cells at a concentration of 10^{-4} M and can thus be considered marginally active in vitro.⁴²⁷

V. EXPERIMENTAL

1. General Methods.

P.m.r. spectra were determined in chloroform-d or dimethyl sulfoxide-d₆ with tetramethylsilane as the standard (set at $\delta=0$) by using a Varian T60, Varian XL-100 or Bruker 270 spectrometer. Values given for coupling constants are first order. Carbon-13 n.m.r. spectra were determined in deuterium oxide with tetramethylsilane as the internal standard by using a Varian CFT-20 spectrometer. Optical rotations were measured at ambient temperature with a Perkin-Elmer Model 141 automatic polarimeter. The c.d. measurements were performed on a Jasco J-20 automatic recording spectropolarimeter and i.r. spectra were recorded on a Perkin-Elmer 710 or 727B spectrometer. All melting points were done on a Leitz microscope heating stage, Model 350, and are corrected. Mass spectra were determined on a HMS-9 spectrometer. Ultraviolet spectra were recorded on a Cary 15 spectrometer. Elemental analyses were performed by Mr. P. Borda of the Microanalytical Laboratory of the University of British Columbia.

2. Chromatography

2.1. Column Chromatography

Silica gel column chromatography was performed using silica gel H for t.l.c. (Merck). If not stated, the ratio of material to absorbent was approximately 1:100 and the ratio of column length to diameter was approximately 10:1. Columns were pressurized above the solvent reservoir at 5-10 p.s.i. providing

flow rates of 70-140 ml h⁻¹.

2.2. Thin Layer Chromatography

All thin layer chromatography was performed using silica gel (Camag) containing 5% calcium sulfate. Compounds were detected by ultraviolet absorption, by spraying with 50% sulfuric acid followed by heating on a hot plate, or by spraying with a 0.3% solution of ninhydrin in n-butanol followed by warming at 110° in an oven.

3. Abbreviations.

The abbreviations used in the following descriptions are as follows: n.m.r. (nuclear magnetic resonance), u.v. (ultraviolet), i.r. (infrared), m.p. (melting point), t.l.c. (thin layer chromatography), c.d. (circular dichroism), DMF (N,N-dimethylformamide), DMSO (dimethyl sulfoxide), THF (tetrahydrofuran), MeOH (methanol), s (singlet), d (doublet), d d (doublet of doublets), t (triplet), q (quartet).

4. Synthesis of Glycos-3-yl Amino Acids

1,2:5,6-Di-O-isopropylidene- α -D-ribo-hexofuranos-3-ulose (14). - To a mechanically-stirred solution of 1,2:5,6-di-O-isopropylidene- α -D-glucO-furanose^{33a} (261, 20g) in carbon tetrachloride (100 ml) and water (100 ml) containing sodium hydrogen carbonate (1g) and ruthenium dioxide (hydrate, 0.2g), was very slowly added a 5% solution of sodium metaperiodate (1 ml every 10 min) until the characteristic yellow-green colouration of ruthenium tetraoxide was observed. When the

solution had completely reverted to the black, dioxide stage the addition was repeated as above. After 1 h, the rate of addition was increased to 1 ml per minute and after 4 hours the solution could be stirred with an excess of periodate present. The pH of the mixture was maintained at greater than 6 by the addition of sodium hydrogen carbonate. After 10-20 hours the reaction was complete as evidenced by t.l.c. on silica gel eluted with 95:5 dichloromethane-ethyl acetate. Excess ruthenium tetroxide was decomposed by the addition of isopropanol (1 ml). The reaction mixture was filtered and the carbon tetrachloride layer separated from the aqueous solution. The latter was then extracted with chloroform (10 x 100 ml). The combined organic solutions were washed with 5% sodium thiosulfate solution (50 ml), dried over anhydrous sodium sulfate, filtered and evaporated to afford crystalline ketose hydrate 262 (19.5 grams, 97%). Compound 262 was recrystallized from water-saturated ethyl acetate and hexane; m.p. 109-110° (lit.⁴¹⁹ m.p. 109-111°). Immediately before use, the anhydrous ketose 14 was prepared by azeotropic distillation with toluene.

3-C-[(R,S)-Cyano(ethoxycarbonyl)methylene]-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (264). A mixture of 1,2:5,6-di-O-isopropylidene- α -D-ribo-hexofuranos-3-ulose (14) (6.2 g, 24 mmol), ethyl cyanoacetate (263, 2.7 g, 24 mmol), and ammonium acetate (5 mg) in anhydrous DMF (100 ml) was stirred for 2 hours at room temperature. The reaction mixture was then poured into ice-water (1 l) and extracted with chloroform (6x100 ml). The combined chloroform extracts were dried with magnesium sulfate

and evaporated, leaving a crude syrup which was chromatographed on silica gel (200 g) using 2:1 benzene-ethyl acetate as developer. A fluorescent compound of R_f 0.54, consisting of a mixture of 265 and 266 (0.9 g) was first eluted followed by compound 264 (R_f 0.44, 875 mg, 26%). The latter was crystallized from ether-hexane, m.p. 97-99°; $[\alpha]_D^{23} + 80.4^\circ$ (c 3.4, chloroform); $\nu_{\text{max}}^{\text{CCl}_4}$ 3525 (-OH), 2260 (-C≡N), and 1730 cm^{-1} (ester C=O); n.m.r. (CDCl_3); δ 1.37 (t, 3H, CH_2CH_3), 1.30, 1.34, 1.50, 1.62 (s, 12H, 4x CH_3), 4.07 (d, 1H, $J_{\text{OH,CH}}$ 1.0 Hz, OH, exchanges in D_2O), 4.57 (d, 1H, $J_{1,2}$ 4.0 Hz, H-2), 5.93 (d, 1H, H-1); mass spectrum: m/e 356 (M^+-CH_3).

Anal. Calc. for $\text{C}_{17}\text{H}_{25}\text{NO}_8$: C, 54.99; H, 6.74; N, 3.77.
Found: C, 54.67; H, 6.49; N, 3.64.

3,3-C-Bis[(RS,SS,RR)-cyano(ethoxycarbonyl)methyl]-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (266) and 3-C-[(R,S)-cyano(ethoxycarbonyl)methylene]-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (268). - To the syrupy mixture of 265 and 266 (600 mg) in methanol (15 ml) was added Analar Indicator in H_2O to turn the solution yellow (pH 4.0). Sodium cyanoborohydride (100 mg), dissolved in methanol, was then added at room temperature and the yellow colour of the reaction mixture maintained by intermittent addition of 1% HCl in methanol. After the reaction mixture was stirred for 30 min, t.l.c. monitoring of the product on silica using 10:1 benzene-ethyl acetate as developer showed two non-fluorescent compounds of R_f 's 0.15 and 0.20. The solution was neutralized with aqueous sodium hydrogen carbonate. The aqueous fraction was extracted

with chloroform (3x20 ml), and the combined organic fractions were dried with sodium sulfate, and the solvents evaporated under reduced pressure. The residual syrup was chromatographed on a column of silica gel (200 g) using 10:1 benzene-ethyl acetate as developer, yielding 266 (268 mg) which was crystallized from ether-hexane, m.p. 136-140°; n.m.r. (CDCl₃): δ 1.20-1.58 (m, 18 H, 4xCH₃, 2xCH₂CH₃), 6.02 (d, 1H, J_{1,2} 5.0 Hz, H-1); and 268 as a solid (220 mg) m.p. 50-52°; $[\alpha]_D^{23} + 79.4^\circ$ (c 1.2, chloroform); n.m.r. (CDCl₃): δ 1.30 (t, 3H, CH₂CH₃), 1.25, 1.40, 1.50, 1.55 (s, 12H, 4xCH₃), 2.34-2.70 (m, 7H, H-4, H-5, H-6, CH₂CH₃, CHCN), 4.78 (pseudo-t, 1H, J_{2,3} 5.0 Hz, H-2), 5.78 (d, 1H, J_{1,2} 4.0 Hz, H-1).

Anal. of 266. Calc. for C₂₂H₃₂N₂O₉: C, 56.66; H, 6.44; N, 6.00. Found: C, 56.58; H, 6.65; N, 5.85.

Anal. of 268. Calc. for C₁₇H₂₅N O₇: C, 57.47; H, 7.04; N, 3.94. Found: C, 57.18; H, 7.19; N, 3.68.

3-C-[(R,S)-Acetamidomethyl(ethoxycarbonyl)methylene]-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (270). - A solution of compound 264 (0.31 g, 0.85 mmol) in dry acetic anhydride (6 ml) was hydrogenated at 3 atm for 10 h in the presence of platinum oxide (Adam's catalyst, 20 mg). The catalyst was then removed by filtration, xylene (10 ml) added to the filtrate, and the solution evaporated under reduced pressure. The residue was chromatographed on a column of silica gel (30 g) using 9:1 benzene-ethanol as developer giving 270 as a syrup (0.34 g, 96%); $[\alpha]_D^{23} + 62.6^\circ$ (c 2.7, chloroform); n.m.r. (CDCl₃): δ 1.08-1.58 (m, 15H, 4xCH₃, CH₂CH₃), 1.92-1.94 (d, 3H, COCH₃), 4.40 (d, 1H, J_{1,2} 3.8 Hz, H-2), 5.73 (d, 1H, H-1), 6.10-6.52 (d(broad),

1H, NH); mass spectrum: m/e 417 (M^+), 345 ($M^+ - CH_3CONHCH_2$).

Anal. Calc. for $C_{19}H_{31}NO_9$: C, 54.68; H, 7.43; N, 3.36.

Found: C, 54.38; H, 7.20; N, 3.13.

3-C-[(R,S)-Cyanofethoxycarbonyl]methylene]-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-erythro-hex-3-enofuranose (273). - To a solution of compound 264 (216 mg) in anhydrous pyridine (8 ml) at 0° was added a solution of freshly distilled thionyl chloride (0.5 ml) in pyridine (2 ml). The reaction mixture was stirred for 3 min at 0° and then poured into a mixture of ice water-chloroform. The chloroform layer was drawn off, the water layer washed once with chloroform and the combined chloroform extracts washed once with water and dried with sodium sulfate. The organic solvents were evaporated in vacuo, traces of pyridine being removed by azeotropic distillation with xylene at reduced pressure, leaving a yellow syrup (188 mg). The latter was chromatographed on silica gel (20 g) using 15:1 benzene-ethyl acetate as developer, yielding compound 273 as a clear syrup (60 mg, 30%); $[\alpha]_D^{25} + 110.6^\circ$ (c 1.9, chloroform); $\nu_{\max}^{CHCl_3}$ 2240 ($-C \equiv N$), 1740 (ester $-C=O$), 1698 cm^{-1} ($-C=C-$); λ_{\max}^{MeOH} 212, 263 nm (c 0.02); n.m.r. ($CDCl_3$): δ 1.26-1.62 (m (9 lines), 15H, $4 \times CH_3$, CH_2CH_3), 3.88-4.44 (m, 4H, H-6, CH_2CH_3), 4.60-4.82 (t, 1H, $J_{5,6}$ 6.5 Hz, H-5), 5.40 (d, 2H, H-2, $CHC=O$), 6.02-6.12 (dd, 1H, H-1); n.m.r. (benzene- d_6): δ 0.84-1.08 (dd, 3H, CH_2CH_3), 1.24-1.62 (m (6 lines), 12H, $4 \times CH_3$), 3.80-4.18 (m, 4H, H-6, CH_2CH_3), 4.34-4.52 (t (broad), 1H, H-5), 5.20 (d, $J_{1,2}$ 6Hz, 0.6H, R (or S) H-2), 5.30 (s, 0.6H, R (or S) $-CHC=O$), 5.40 (d, 0.4H, S (or R) H-2), 5.45 (s, 0.4H, S (or R) $-CHC=O$), 5.57 (d, 0.6H, R (or S) H-1), 5.70 (d, 0.4H, S (or R) H-1).

Anal. Calc. for $C_{17}H_{23}NO_7$: C, 57.79; H, 6.52; N, 3.97.
Found: C, 57.69; H, 6.39; N, 4.10.

2-Lithio-1,3-dithiane¹⁹² (126). - To a solution of 1,3-dithiane (123, dried by azeotropic distillation with benzene) in anhydrous THF at -78° under nitrogen was added dropwise a solution of 1.6 M n-butyllithium in hexane (1 equivalent). After completion of the addition, the mixture was stirred at -78° for 30 min and then stored at -20° for 3-4 h prior to use in other reactions.

3-C-(1,3-Dithian-2-yl)-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (176). - A solution of the ketose 14 (4.95 g) in THF (50 ml) was added at -78° under nitrogen to a solution of the dithiane anion 126 (2.64 g) in THF (40 ml). After 2.5 h at -20° , the reaction mixture was quenched with water (200 ml) and the solution was extracted with chloroform (3x200 ml). The combined organic extracts were dried with sodium sulfate and evaporated leaving a crude syrup (5.8 g). Unreacted 1,3-dithiane was removed by sublimation and the residue was crystallized from ether-hexane yielding colourless crystals of 176 (3.8 g, 57%); m.p. $96-97^\circ$ (lit.²³⁶ m.p. 97°); n.m.r. (60 MHz, $CDCl_3$): δ 5.82 (d, 1H, H-1), (lit.²³⁶ δ 5.98, d, H-1).

3-C-Formyl-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (278) and its semicarbazone 279. - A mixture of the dithianyl compound 176 (40 mg), methyl iodide (1 ml), and barium carbonate (60 mg) in 10% aqueous acetone (10 ml) was held at 55° for 12 h after which it was cooled and filtered to remove the

barium salts. The filtrate was evaporated under reduced pressure. The resulting solid was then dissolved in chloroform (30 ml) and washed with water (5 ml). After the chloroform layer was dried with sodium sulfate, the solvent was evaporated to yield a crude syrup (28 mg, 92%) identified as the aldehyde 278;
 $\nu_{\text{max}}^{\text{CHCl}_3}$ 3400 (OH), 1720 cm^{-1} (C=O); n.m.r. (100 MHz, CDCl_3): δ 9.86 (s, 1H, HC=O). Without further purification, 278 was dissolved in methanol (2 ml) and pyridine (0.5 ml) following which semicarbazide hydrochloride (0.5 ml of a 2M aqueous solution) was added to the solution. The mixture was heated on a steam-bath for 5 min, diluted with water (20 ml) and extracted with ethyl acetate (3x15 ml). The combined organic extracts were then dried with sodium sulfate, evaporated in vacuo and the residue chromatographed on a column of silica gel (20 g) using 9:1 benzene-ethyl acetate as the developer, yielding a major component (279) as a solid (15 mg, 42%) which was crystallized from benzene-ethanol; m.p. 227-228°; $[\alpha]_{\text{D}}^{23} +78.3^\circ$ (c 0.84, methanol); n.m.r. (100 MHz, DMSO-d_6): δ 1.28, 1.32, 1.49 (s, 12H, 4x CH_3), 3.63 (dd, 1H, $J_{6a,6b}$ 9.0 Hz, $J_{5,6a}$ 6.0 Hz, H-6a), 3.86 (dd, 1H, $J_{5,6b}$ 5.0 Hz, H-6b), 4.02-4.16 (m, 2H, H-4, H-5), 4.63 (d, 1H, $J_{1,2}$ 4.0 Hz, H-2), 5.58 (s, 1H, OH, exchangeable with D_2O), 5.83 (d, 1H, H-1), 6.40 (broad s, 2H, NH_2 , exchangeable with D_2O), 7.12 (s, 1H, CH=N), 10.04 (broad s, 1H, NH, exchangeable with D_2O).

Anal. Calc. for $\text{C}_{14}\text{H}_{23}\text{N}_3\text{O}_7$: C, 48.70; H, 6.67; N, 12.17.
 Found: C, 48.73; H, 6.67; N, 11.92.

3-C-(2,4-Diketotetrahydroimidazol-5-(R,S)-yl)-1,2:5,6-di-O-isopropylidene- α -D-allofuranose (280). -A mixture of the

aldehyde 278 (0.67 g), freshly-recrystallized ammonium carbonate (1.11 g) and sodium cyanide (0.53 g) in methanol (30 ml) was stirred under 3 atmospheres of carbon dioxide for 3 h at 20° and then for 18 h at 55°. The reaction mixture was then cooled, filtered and the filtrate was evaporated under reduced pressure. The residual solid was then dissolved in water (20 ml) and the solution was acidified to pH 6.5 by addition of 3N hydrochloric acid. Extraction of the aqueous solution with ethyl acetate (3x20 ml), drying of the combined organic extracts with sodium sulfate and evaporation of the solvents left a crude solid which was chromatographed on silica gel (30 g) using 9:1 benzene-ethyl acetate as the developer. The component of R_f 0.06 (280) was thus isolated as a solid (440 mg, 53%) which was crystallized from benzene-ethanol, m.p. 282-283°; $[\alpha]_D^{23} +29.0^\circ$ (c 0.7, methanol); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3400 (broad, OH, NH), 1780 (C=O), 1700 cm^{-1} (C=O); n.m.r. (100 MHz, DMSO- d_6): δ 1.28, 1.32, 1.50 (s, 12H, 4xCH₃), 3.80-4.10 (m, 2H, H-6), 4.20-4.34 (m, 2H, H-4, H-5), 4.26 (s, 1H, H-1', sharpens upon addition of D₂O), 4.44 (d, 1H, J_{1,2} 3.5 Hz, H-2), 5.66 (d, 1H, H-1), 7.60, 7.86, 8.16 (broad s, 3H, OH, NH, all exchangeable with D₂O).

Anal. Calc. for C₁₅H₂₂N₂O₈: C, 50.28; H, 6.15; N, 7.82. Found: C, 50.73; H, 6.23; N, 8.07.

D- and L-2-(1,2:5,6-Di-O-isopropylidene- α -D-allofuranos-3-yl)glycine (281). -A suspension of the hydantoate 280 (47 mg) in saturated aqueous barium hydroxide (6 ml) was refluxed at 125° for 4 h. Ammonium carbonate (1 g) was added in portions and the solution was refluxed for another 30 min. The barium salts were then removed by filtration, the filtrate was concentrated

under reduced pressure and applied to a column (31x2.25 cm) of Bio-Rex 70 (H⁺) cation exchange resin. Elution with water and collection of the ninhydrin positive fractions yielded 281 as a hard glass (32 mg, 74%); $[\alpha]_D^{23} +43.2^\circ$ (c 2.13, water), (lit.³⁵⁸ $[\alpha]_D^{25}$ of L-isomer: $+89.2^\circ$ (water); D-isomer $+25^\circ$ (water)); R_f 0.65 (Whatman #1 paper, 10:4:3 ethyl acetate-pyridine-water, ninhydrin detection); ν_{\max}^{KBr} 3400 (OH, NH₂), 1725 (C=O), 1600 cm⁻¹ (NH₂); n.m.r. (100 MHz, D₂O): δ 1.42, 1.48, 1.60 (s, 12H, 4xCH₃), 5.88 (d, 2/3 H, $J_{1,2}$ 3.5 Hz, H-1 of D-isomer), 5.93 (d, 1/3 H, $J_{1,2}$ 3.5 Hz, H-1 of L-isomer) (lit.³⁵⁸ δ 6.07 (H-1 of D-isomer), 6.08 (H-1 of L-isomer), $J_{1,2}$ 3.5 Hz for L and D); mass spectrum: m/e 318 (M⁺-CH₃), 260 (M⁺-glycine).

Anal. Calc. for C₁₄H₂₃NO₈·H₂O: C, 47.86; H, 7.12; N, 3.99. Found: C, 48.13; H, 7.40; N, 4.11.

Crystallization of 281 from ethanol-ethyl acetate gave a small quantity of the L-glycine isomer (2 mg), m.p. 192-193° (lit.³⁵⁸ m.p. 189-191°).

5. Synthesis of Precursors to C-Nucleosides.

2,5-Anhydro-3,4,6-tri-O-benzoyl-D-allose (203). - A solution of p-toluenesulfonic acid monohydrate (0.92 g) in acetone (25 ml) was added dropwise to an ice-cooled solution of 1,3-diphenyl-2-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)imidazolidine^{272 423} (204, 1.5 g) in methylene chloride (75 ml). After 5 min at room temperature, the reaction mixture was gradually allowed to come to room temperature and was stirred for another 30 min. T.l.c. (2:1 ether-hexane) of the product at this time showed complete reaction. The mixture was

then filtered, the precipitate was washed with methylene chloride and the combined filtrates were evaporated under reduced pressure at a temperature not exceeding 30°. The residue was dissolved in methylene chloride (100 ml), washed with water (3x20 ml), and the organic layer was dried with magnesium sulfate. Evaporation of the solvents left 203 as a syrup (1.02 g, 96%); n.m.r. (60 MHz, CDCl_3): δ 9.72 (d, approx 1H, $J_{1,2}$ 1.5 Hz, H-C=O), (lit.²⁷² δ 9.77, $J_{1,2}$ 1.5 Hz).

Ethyl (E or Z)-4,7-anhydro-2-cyano-2,3,5-trideoxy-6,8-di-O-benzoyl-erythro-octon-2,4-dieneate (283). - A mixture of 2,5-anhydro-3,4,6-tri-O-benzoyl-D-allose (203, 1.02 g, 2.15 mmol), ethyl cyanoacetate (263, 250 mg, 2.2 mmol) and ammonium acetate (30 mg) in anhydrous DMF (20 ml) was stirred at 0° for 6 h. After the reaction mixture was poured into ice-water (100 ml), the mixture was extracted with chloroform (3x50 ml). The combined organic extracts were dried with sodium sulfate and evaporated under reduced pressure. The resulting crude syrup (1.35 g) was chromatographed on a silica gel column (130 g) using 10:1 benzene-ethyl acetate as developer. Compound 283 (300 mg, 31%) was crystallized from ether, m.p. 124-127°; $[\alpha]_D^{23} +244.40$ (c 0.7, chloroform); $\nu_{\text{max}}^{\text{CHCl}_3}$ 2270 ($\text{C}\equiv\text{N}$), 1720 (ester C=O), 1630 and 1600 cm^{-1} (C=C); n.m.r. (CDCl_3): δ 1.38 (t, 3H, CH_2CH_3), 4.30 (q, 2H, CH_2CH_3), 4.60-4.75 (d, 2H, H-8), 5.04 (m, 1H, H-7), 6.12 (2s, 2H, H-3, H-5); mass spectrum: m/e 325 ($\text{M}^+ - \text{C}_6\text{H}_5\text{COOH}$), 204 ($\text{M}^+ - 2\text{C}_6\text{H}_5\text{COOH}$).

Anal. Calc. for $\text{C}_{25}\text{H}_{21}\text{NO}_7$: C, 67.11; H, 4.70; N, 3.13. Found: C, 66.83; H, 4.78; N, 3.07.

Ethyl 4,7-anhydro-2-(R,S)-acetamidomethyl-6,8-di-O-benzoyl-2,3,5-trideoxy-4-(R,S)-D-erythro-D-octonate (284). - A solution of compound 283 (710 mg, 1.6 mmol) in dry acetic anhydride (30 ml) was hydrogenated over platinum oxide (140 mg) at 3 atm for 20 h at room temperature. The catalyst was removed by filtration and the filtrate evaporated at reduced pressure to yield an oil which was chromatographed on a silica gel column (130 g) using 9:1 benzene-ethanol as developer. The product having R_f 0.25 (284) was isolated as a syrup (250 mg, 31%); $[\alpha]_D^{25} +2.3^\circ$ (c 0.4, chloroform); $\nu_{\text{max}}^{\text{CHCl}_3}$ 1720 (ester C=O), 1660 (amide C=O); n.m.r. (CDCl_3): δ 1.14-1.37 (q, 3H, CH_2CH_3), 1.95 (s, 3H, Ac), 5.45-6.10 (d(broad), 1H, NH), 7.39-8.06 (m, 10, $2 \times \text{C}_6\text{H}_5$); mass spectrum: m/e 497 (M^+), 375 ($M^+ - \text{C}_6\text{H}_5\text{COOH}$); also seen in the mass spectrum were peaks at m/e 503 and 509 indicating saturation of one and two phenyl rings of 284.

Anal. Calc. for $\text{C}_{27}\text{H}_{31}\text{NO}_8$: C, 65.19; H, 6.24; N, 2.82. Found: C, 65.27; H, 6.30; N, 2.60.

2,3-O-Isopropylidene-5-O-trityl- β -D-ribofuranosyl chloride (210). - A solution of 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose³⁶² (285, 13.4 g) in anhydrous N,N-dimethylformamide (20 ml) was treated with carbon tetrachloride (15 g) and triphenylphosphine (7 g) for 14 h at room temperature. The solution was then poured into a rapidly stirring mixture of diethyl ether (50 ml), hexane (50 ml) and ice-water (100 ml). The suspension was quickly filtered through a Celite pad to remove insoluble triphenylphosphine oxide and the aqueous layer was separated. The organic layer was dried over sodium sulfate and evaporated in vacuo to give a clear syrup. Addition of

benzene to the syrup precipitated residual triphenylphosphine oxide which was removed by filtration. Hexane was then added to the filtrate until cloudiness was observed whereupon crystallization commenced, finally yielding the glycosyl chloride 210 (5.6 g, 40%) in two crops; m.p. 113-116°, (lit.³⁶² m.p. 114-115°); n.m.r. (60 MHz, CDCl_3): δ 6.08 (s, 1H, H-1), (lit.³⁶² δ 6.10, s, H-1). The chloride 210 was generally used in its syrup form rather than its crystalline form in subsequent reactions in order to avoid losses due to decomposition.

Diethyl sodium phthalimidomalonate (61). - A solution of diethyl phthalimidomalonate⁴²⁰ (286, 15 g) in anhydrous diethyl ether (50 ml) was added slowly under nitrogen to a rapidly stirring suspension of sodium hydride (2.4 g of a 50% dispersion in oil) in diethyl ether (200 ml). After one hour, the yellow precipitate of 61 which had formed was collected by filtration, washed copiously with dry ether, and stored in a desiccator (13.5 g, 84%); n.m.r. (60 MHz, DMSO-d_6): δ 0.80 (t, 6H, CH_2CH_3), 3.65 (q, 4H, CH_2CH_3), 7.60 (s, 4H, Ar).

Diethyl 2,3-O-isopropylidene-5-O-trityl- α -(and β)-D-ribofuranosyl phthalimidomalonate (287 and 288, respectively). -

A solution of the glycosyl chloride 210 (0.62 g) and diethyl sodium phthalimidomalonate (61, 0.44 g) in anhydrous N,N-dimethylformamide (100 ml) was maintained at 90° for 5 h under an atmosphere of dry nitrogen. The reaction mixture was cooled, poured into rapidly-stirring ice-water (100 ml) and the water was extracted with chloroform (3x100 ml). The combined chloroform extracts were dried with magnesium sulfate, the

solvents were evaporated under reduced pressure, and the residue was chromatographed on silica gel (130 g) using 10:1 benzene-ethyl acetate as the developer, yielding a 1:1 mixture of 287 and 288 as a white foam (0.45 g, 46%); $[\alpha]_D^{23} +12.5^\circ$ (c 0.9, chloroform); $\nu_{\text{max}}^{\text{CHCl}_3}$ 1755 (ester), 1725 cm^{-1} (amide); n.m.r. (60 MHz, CDCl_3): δ 1.21 (t, 6H, CH_2CH_3), 1.29, 1.37 (s, 6H, $2 \times \text{OCH}_3$), 3.10 (m, 2H, H-5'), 3.80-4.60 (m, 7H, H-2', H-3', H-4', CH_2CH_3), 5.03 (d, approx. 0.5 H, $J_{1,2}$ 3.5 Hz, H-1' of α -anomer), 5.08 (s, approx. 0.5 H, H-1' of β -anomer), 6.90-7.40 (m, 15H, trityl), 7.60 (m, 4H, phthalyl); mass spectrum: 705.254 ($\text{MH}^+ - \text{CH}_3$). $\text{C}_{41}\text{H}_{39}\text{O}_{10}\text{N}$ requires 705.257.

Anal. Calc. for $\text{C}_{42}\text{H}_{41}\text{NO}_{10}$: C, 70.10; H, 5.70; N, 1.95. Found: C, 70.27; H, 5.84; N, 1.78.

Attempted Unblocking of 287 and 288. - A mixture of 287 and 288 (424 mg) in methanol (10 ml) containing 1N aqueous sodium hydroxide (1 ml) was refluxed for 3 h. The reaction mixture was cooled, 2N hydrochloric acid (2 ml) was added and the solution was refluxed for another 4 h. Cooling of this reaction mixture resulted in the precipitation of triphenylcarbinol (15 mg) which was collected by filtration, m.p. 155-159°, (lit.⁴²⁵ m.p. 164.2°); n.m.r. (100 MHz, MeOH-d_4): δ 7.80-8.12 (m, Ar). The filtrate was neutralized with 1N sodium hydroxide and concentrated under reduced pressure. The residue was then chromatographed on a column of Bio-Rex 70 (H^+) resin (30x2.75 cm) using water as the developer. The ninhydrin-positive fractions were collected and evaporated. An n.m.r. spectrum of the residue (20 mg, 16%) in D_2O showed only a complex multiplet at δ 3.40-4.10.

6. Attempted Synthesis of C-Nucleosides Using a Palladium Catalyst.

5-Bromo-2,4-dichloropyrimidine (291). - A suspension of 5-bromouracil³⁶⁷ (290, 4.4 g) in phosphorus oxychloride (15 ml) was heated at 125° for 5 days. The homogeneous reaction mixture was then cooled and the solvent was removed by distillation under reduced pressure. Ice-water (100 ml) was carefully added to the resulting syrup and the mixture was extracted with ether (2x50 ml). The ether extracts were dried with sodium sulfate, the ether evaporated and the remaining yellow syrup was distilled at 60° at 0.2 torr to afford 291 as a clear oil (3.17 g, 61%), (lit. b.p. 145-147° (78 mm)).

5-Bromo-2,4-di-t-butoxypyrimidine (292). - Dry t-butanol (25 ml) in anhydrous hexane (10 ml) was added to a stirred suspension of sodium hydride (1.4 g of a 50% dispersion in oil) in hexane (15 ml). After 5 min reaction at room temperature, the solution was refluxed for 10 min. The resulting suspension of sodium t-butoxide was cooled and a solution of 5-bromo-2,4-dichloropyrimidine (291, 3 g) in hexane (10 ml) was added slowly to maintain reflux. After complete addition of 291, the reaction mixture was refluxed for 2 h before it was cooled and evaporated. Water was added to the residue and the mixture was extracted with ether (5x20 ml). The combined ether extracts were dried with magnesium sulfate, the ether evaporated and the residue distilled at 0.2 torr. The fraction distilling at 60° was discarded while that distilling at 80-100° was collected. The latter fraction crystallized spontaneously at room temperature to give pure 292 (2.55 g, 65%); m.p. 55-57°.

(lit.²⁹³ m.p. 63-64°); n.m.r. (60 MHz, CDCl_3); δ 1.55 (s, 9H, $3\times\text{CH}_3$), 1.60 (s, 9H, $3\times\text{CH}_3$), 8.10 (s, 1H, H-6); mass spectrum: m/e 302 (M^+).

2,4-Di-t-butoxy-5-magnesiumbromopyrimidine (294) and 5-(1-propen-2-yl)uracil (296). - A solution of the bromo derivative 292 (375 mg, 1.24 mmol) and ethyl bromide (1.35 mg, 1.24 mmol), in anhydrous tetrahydrofuran (THF, 4 ml) was added over 30 min to a mixture of magnesium powder (90 mg, 3.72 gr. at.) in refluxing THF (2 ml) under an atmosphere of dry nitrogen. This solution of the 5-magnesiumbromo derivative 294 was refluxed for 1 h after completion of the addition and then cooled before acetone (230 mg, 4 mmol) in anhydrous ether (5 ml) was added dropwise. After the vigorous reaction had subsided, the mixture was refluxed for an additional 30 min, cooled, and poured into water (100 ml) to which had been added hydrochloric acid (5 ml of a 0.2M solution). The aqueous mixture was extracted with ether (3x50 ml), the combined organic extracts washed with saturated aqueous sodium hydrogen carbonate, dried with magnesium sulfate and evaporated under reduced pressure. The resulting crude syrup, containing unreacted 292 as evidenced by t.l.c. on silica gel was distilled (60°, 0.2 torr), leaving a residue (295, $\nu_{\text{max}}^{\text{CHCl}_3}$ 3650 cm^{-1} (OH)) which, without further purification, was hydrolyzed by refluxing for 5 min in methanol containing conc. HCl (0.2 ml). Evaporation of the solvents then left a yellowish solid which was crystallized from ethanol to afford 296 (82 mg, 43%); m.p. 300-315° (decomp.); n.m.r. (100 MHz, $\text{DMSO}-d_6$): δ 1.92 (s, 3H, CH_3), 5.01 (dd, 1H, $J_{1a,1b}$ 2 Hz, J_{1a,CH_3} 1Hz, H-1a), 5.79 (d, 1H, H-1b), 7.35 (s, 1H, H-6), 11.00

(broad s, 2H, NH, exchangeable with D₂O); mass spectrum: m/e 152 (M⁺), 137 (M⁺-CH₃).

Anal. Calc. for C₇H₈N₂O₂·1/3 H₂O: C, 53.11; H, 5.48; N, 17.72. Found: C, 53.12; H, 5.20; N, 18.30.

Iodo(phenyl)bis(triphenylphosphine)palladium (II) (298). -

A solution of freshly-distilled phenyl iodide (300 mg) in benzene (50 ml) was added dropwise to a rapidly stirred suspension of tetrakis(triphenylphosphine)palladium (0)⁴²⁴ (226, 1.5 g). The resulting dark orange solution was stirred for 10 min after completion of the addition, after which the solvents were evaporated. The residual solid was then triturated with ether and the precipitate was collected by filtration. Crystallization of this solid from methylene chloride-hexane gave orange needles of 298 (320 mg, 30%); m.p. 195-197° (decomp.), (lit.³⁷⁰ m.p. 171-186° (decomp.)).

Attempted Palladium (II)-catalyzed Coupling of 210 and 294. - To a refluxing solution of the glycosyl chloride 210 (610 mg) in anhydrous THF (10 ml) containing the palladium (II) catalyst 298 (20 mg) was added, under an atmosphere of dry nitrogen, a solution of the Grignard reagent 294 (350 mg) in THF (8 ml). The reaction mixture was refluxed for 12 h by which time all starting sugar had been consumed as shown by t.l.c. on silica gel. The solvents of the mixture were next evaporated, ether was added to the residue and the insoluble material removed by filtration. T.l.c. of the filtrate using 10:1 benzene-ethyl acetate showed many components, only two of which were fluorescent and charring. These were isolated by column

chromatography on silica gel using 10:1 benzene-ethyl acetate as the developer in yields of 30 mg and 40 mg. However, neither of the n.m.r.'s of these two sugar components displayed peaks associated with the blocked pyrimidine 303, indicating that coupling had not occurred.

7. Synthesis of 6-Substituted Nucleosides.

2,2'-Anhydro-1-(5-O--trityl- β -D-arabinofuranosyl)uracil (307). - Following the method of Fox and Wempen³⁷⁴, a mixture of 5'-O-trityluridine³⁷³ (305, 13.6 g) and thiocarbonyldiimidazole (306, 5.6 g) in anhydrous toluene (500 ml) was refluxed at 120° for 1 h. The precipitate which formed was collected by filtration, washed with toluene, dried in vacuo and recrystallized from methanol, yielding 307 as shiny plates (11.5 g, 88%); m.p. 222-223°, (lit.³⁷⁴ m.p. 219-221°).

2,2'-Anhydro-1-(3-O-acetyl-5-O-trityl- β -D-arabinofuranosyl)uracil (308). - In a modification of the procedure of Ogilvie and Iwacha,⁴²¹ a solution of the tritylated anhydronucleoside 307 (10 g) and acetic anhydride (30 ml) in anhydrous pyridine (100 ml) was stirred at room temperature for 18 h, following which the solvents were evaporated at reduced pressure, the temperature of the mixture never exceeding 35°. Residual acetic anhydride was removed from the crude product by repeated azeotropic distillation with xylene. The glassy residue was then passed through a short column of silica gel (200 g) using 5:1 benzene-ethyl acetate as the eluting solvents. The acetate 308 was thus obtained as a white foam (10.5 g, 96%);

$[\alpha]_D^{23} -28.9^\circ$ (c 1.5, methanol); n.m.r. (100 MHz, $CDCl_3$): δ 2.10 (s, 3H, CH_3), 3.01 (dd, 2H, $J_{4',5'} 7.0$ Hz, $J_{5'a,5'b} 0.5$ Hz, H-5'), 4.45 (t of doublets, 1H, $J_{3',4'} 1.5$ Hz, H-4'), 5.30 (d, 1H, $J_{1',2'} 6.0$ Hz, H-2'), 5.40 (d, 1H, H-3'), 5.84 (d, 1H, $J_{5,6} 8.0$ Hz, H-5), 6.25 (d, 1H, H-1'), 7.15-7.50 (m, 16H, H-6, Ar).

Anal. Calc. for $C_{30}H_{26}N_2O_6 \cdot 1/3 H_2O$: C, 69.77; H, 5.16; N, 5.42. Found: C, 70.05; H, 4.94; N, 5.36.

Synthesis of 2-(1,3-dithian-2-yl)-1-(5-O-trityl- β -D-arabinofuranosyl)-4(1H)-pyrimidinone (309) and 2,2'-anhydro-5,6-dihydro-6-(S)-(1,3-dithian-2-yl)-1-(5-O-trityl- β -D-arabinofuranosyl)uracil (310). - A solution of anhydronucleoside 308 (1.2 g, 2.5 mmole) in anhydrous THF (20 ml) was added by syringe to a solution of the dithiane anion 126 (1.5 g, 12.5 mmoles) in THF at -78° under nitrogen. A yellow precipitate formed immediately and the mixture was stirred at -78° for an additional hour after which water (0.5 ml) in THF (5 ml) was slowly added. Stirring of the mixture was continued at -78° for 30 min. before it was allowed to come to room temperature. The solution, neutralized with dilute hydrochloric acid, was then extracted with chloroform (5x40 ml), the combined organic extracts dried (magnesium sulfate) and the solvents evaporated, leaving a crude orange syrup (1.8 g). Chromatography of this syrup on silica gel (200 g) using 9:1 benzene-ethanol as eluting solvents gave 309 (183 mg, 15%); R_f 0.10; m.p. $155-156^\circ$; $[\alpha]_D^{23} +38.8^\circ$ (c 1.28, methanol); ν_{max}^{KBr} 3380 (OH), 1725 (C=O), 1635 (C=N), and 1600 cm^{-1} (C=C); n.m.r. (100 MHz, $DMSO-d_6$): δ 1.74-2.20 (m, 2H, SCH_2CH_2), 2.95-3.21 (m, 4H, SCH_2CH_2), 3.42 (m, H-5'), 3.80-4.51 (m, 3H, H-2', 3', 4'), 5.46 (s, 1H, SCHS), 5.71 (d,

1H, OH, exchangeable with D₂O), 5.73 (d, 1H, J_{5,6} 8.0 Hz, H-5), 5.92 (d, 1H, OH, exchangeable with D₂O), 6.31 (d, 1H, J_{1',2'} 5.0 Hz, H-1'), 7.31-7.46 (m, 15H, Ar), 7.91 (d, 1H, H-6); mass spectrum: m/e 375 (M⁺ - base).

Anal. Calc. for C₃₂H₃₂N₂O₅S₂•H₂O: C, 63.36; H, 5.61; N, 4.62. Found: C, 63.13; H, 5.52; N, 4.49.

The faster running compound 310 was isolated as a non-crystallizable glass (392 mg, 30%); R_f 0.15; [α]_D²³ -109.3° (c 0.66, chloroform); ν_{max}^{CHCl₃} 3350 (OH), 1702 (C=O), 1595 (C=N) and 1460 cm⁻¹; n.m.r. (100 MHz, CDCl₃): δ 1.80-2.38 (m, 4H, SCH₂CH₂, H-5), 2.64-3.26 (m, 6H, SCH₂, H-5'), 3.88-4.05 (m, 1H, H-6), 4.36-4.46 (m, 3H, SCH₃, H-3', H-4'), 5.18 (d, 1H, J_{1',2'} 5.0 Hz, H-2'), 5.50 (s(broad), 1H, OH, exchangeable with D₂O), 6.25 (d, 1H, H-1'), 7.18-7.58 (m, 15H, Ar).

Anal. Calc. for C₃₂H₃₂N₂O₅S₂: C, 65.31; H, 5.44; N, 4.76. Found: C, 65.31; H, 5.64; N, 4.58.

2-Methyl-1-(5-O-trityl-β-D-arabinofuranosyl)-4(1H)-pyrimidinone (313). - Freshly-activated Raney nickel (100 mg) in ethanol (2 ml) was added to a solution of compound 309 (42 mg) in ethanol (5 ml) and refluxed for 1 h by which time t.l.c. of the reaction mixture on silica gel using 5:1 ethyl acetate-ethanol as developer showed complete disappearance of 309 and formation of a single new lower R_f compound. The reaction mixture was then filtered, the nickel washed repeatedly with hot ethanol and the collected filtrate and washings evaporated, leaving a clear syrup (26 mg). Addition of ethanol to the syrup resulted in formation of white crystals of 313 (26 mg, 33%), m.p. 234-235°, (lit.³¹¹ m.p. 238-239°); n.m.r. (100 MHz, DMSO-

d_6): δ 2.39 (s, 3H, CH_3), 3.83-4.33 (m, 3H, H-2', 3', 4'), 5.67 (d, 1H, OH, exchangeable with D_2O), 5.64 (d, 1H, $J_{5,6}$ 8.0 Hz, H-5), 5.79 (d, 1H, OH, exchangeable with D_2O), 6.02 (d, 1H, $J_{5,6}$ 8.0 Hz, H-6); $[\alpha]_D^{25}$ -40.4° (c 0.65, N,N-dimethylformamide) (lit.³¹¹ $[\alpha]_D^{25}$ -43.2° (c 0.22, N,N-dimethylformamide)); mass spectrum: m/e 375 (M^+ -base), 241 ($\text{M}^+ - (\text{C}_6\text{H}_5)_3\text{C}$).

Anal. Calc. for $\text{C}_{29}\text{H}_{28}\text{N}_2\text{O}_5 \cdot \text{C}_2\text{H}_5\text{OH}$: C, 70.18; H, 6.41; N, 5.28. Found: C, 70.21; H, 5.97; N, 5.30.

Acid hydrolysis of 309 to give arabinose, 2-(1,3-dithian-2-yl)-4-pyrimidinone (314) and triphenylcarbinol. - A solution of 309 (20 mg) in methanol (2 ml) and 80% aqueous acetic acid (0.5 ml) was refluxed for 10 min. The reaction mixture was seen to contain by t.l.c. using 5:1 ethyl acetate-ethanol as developer a high R_f (0.90), fluorescent compound (triphenylcarbinol, yellow when t.l.c. plate was sprayed with 50% sulfuric acid and heated), a fluorescent, non-charring component (314, R_f 0.70) and a charring, non-fluorescent material (arabinose, R_f 0.10). The latter was characterized by paper chromatography (No. 1 Whatman, descending elution with water-saturated n-butanol) of the degradation mixture against authentic arabinose (R_f 0.11, alkaline silver nitrate detection). Addition of aqueous ethanol to the reaction mixture caused crystallization of the 2-substituted base component 314 (1 mg), m.p. 210-215° (decomp); n.m.r. (100 MHz, $\text{DMSO}-d_6$): δ 1.87-2.12 (m, 2H, SCH_2CH_2), 2.68-3.44 (m, 4H, SCH_2), 4.92 (s, 1H, SCHS), 6.31 (d, 1H, $J_{5,6}$ 8.0 Hz, H-5), 8.11 (d, 1H, H-6), 12.51 (s (broad), 1H, NH , exchangeable with D_2O).

Anal. Calc. for $\text{C}_8\text{H}_{10}\text{N}_2\text{OS}_2$: C, 44.85; H, 4.67; N, 13.08.

Found: C, 44.60; H, 4.99; N, 13.28.

2-(1,3-Dithian-2-yl)-1-(2,3-di-O-acetyl-5-O-trityl- β -D-arabinofuranosyl)-4(1H)-pyrimidinone (315). - A solution of the nucleoside 309 (2.04 g) in pyridine (20 ml) and acetic anhydride (5 ml) was maintained at 0° for 12 h by which time t.l.c. of the acetylation mixture on silica gel using 9:1 benzene-ethanol as developer showed a single product (R_f 0.43). The solvents were removed by three azeotropic evaporations with xylene and the residual syrup chromatographed on silica gel (200 g) using 10:10:1 benzene-ethyl acetate-ethanol as eluting solvents, yielding the diacetate 315 as a white foam (2.33 g, 100%); $[\alpha]_D^{25} +45.1^\circ$ (c 1.62, chloroform); n.m.r. (100 MHz, DMSO- d_6): δ 1.90 (s, 3H, Ac), 2.11 (s, 3H, Ac), 2.98-3.20 (m, 4H, SCH₂), 3.39-3.52 (m, 2H, H-5'), 4.16-4.36 (m, 1H, H-4'), 5.34-5.50 (pseudo-t, 1H, H-3'), 5.63 (s, 1H, SCHS), 5.68-5.82 (pseudo-t, 1H, H-2'), 5.91 (d, 1H, $J_{5,6}$ 8.0 Hz, H-5), 6.53 (d, 1H, $J_{1,2}$ 5.6 Hz, H-1'), 7.23-7.53 (m, 15H, Ar), 7.83 (d, 1H, H-6).

Anal. Calc. for C₃₆H₃₆N₂O₇S₂: C, 64.29; H, 5.36; N, 4.17.
Found: C, 64.58; H, 5.50; N, 4.11.

2-(1,3-Dithian-2-yl)-1-(2,3-di-O-acetyl- β -D-arabinofuranosyl)-4(1H)-pyrimidinone (316). - A solution of 315 (1.24 g) in 80% aqueous acetic acid (35 ml) was stirred for 65 h following which evaporation of the solvents of the reaction mixture at room temperature and chromatography of the resulting syrup on silica gel (60 g) using 9:1 benzene-ethanol as developer yielded the detritylated compound 316 as a white glass (356 mg, 45%); R_f 0.13; $[\alpha]_D^{25} +48.3^\circ$ (c 1.0, chloroform); n.m.r.

(100 MHz, DMSO- d_6): δ 1.91 (s, 3H, Ac), 2.12 (s, 3H, Ac), 2.94-3.22 (m, 4H, SCH₂), 3.64-3.82 (m, 2H, H-5'), 3.98-4.16 (m, 1H, H-4'), 5.20-5.31 (pseudo-q, 2H, H-3', 3H, partly exchanges with D₂O), 5.55 (s, 1H, SCHS), 5.68-5.82 (pseudo-t, 1H, H-2'), 6.12 (d, 1H, J_{5,6} 8.0 Hz, H-5), 6.51 (d, 1H, J_{1',2'} 5.8 Hz, H-1'), 8.04 (d, 1H, H-6).

Anal. Calc. for C₁₇H₂₂N₂O₇S₂•1/2H₂O: C, 46.47; H, 5.24; N, 6.38. Found: C, 46.68; H, 5.23; N, 6.10.

2-(1,3-Dithian-2-yl)-1- β -D-arabinofuranosyl-4(1H)-pyrimidinone (317). - To a solution of the diacetate 316 (290 mg, 0.67 mmoles) in anhydrous methanol (15 ml) was added a 0.04 M solution of sodium in methanol (70 μ l). After the reaction mixture had been stirred for 1 h at room temperature, it was neutralized with Bio-Rex 70 (H⁺) weakly-acidic cation-exchange resin, the resin was filtered off and washed with methanol. The filtrate and washings were evaporated under reduced pressure, leaving a white foam (237 mg, 100%): $[\alpha]_D^{23} +82.1^\circ$ (c 1.1, methanol); ν_{\max}^{KBr} 3350 (OH), 1725 (C=O), 1625 (C=N), 1600 cm⁻¹ (C=C); $\lambda_{\max}^{\text{MeOH}}$ 245 nm (ϵ 15,700); n.m.r. (100 MHz, DMSO- d_6): δ 1.55-2.29 (m, 2H, SCH₂CH₂), 2.91-3.21 (m, 4H, SCH₂), 3.57-3.79 (m, 3H, H-4', 5'), 3.79-4.05 (m, 1H, H-3'), 4.37 (q, 1H, H-2'), 5.15 (t, 1H, CH₂OH, exchangeable with D₂O), 5.41 (s, 1H, SCHS), 5.52 (d, 1H, CHOH, exchangeable with D₂O), 5.83 (d, 1H, -CHOH, exchangeable with D₂O), 6.00 (d, 1H, J_{5,6} 7.5 Hz, H-5), 6.24 (d, 1H, J_{1',2'} 5.2 Hz, H-1'), 8.01 (d, 1H, H-6); mass spectrum: m/e 347.0741 (M⁺).

Anal. Calc. for C₁₃H₁₈N₂O₅S₂: C, 45.09; H, 5.20; N, 7.91. Found: C, 44.80; H, 5.45; N, 7.91.

Attempted Hydrolysis of the Dithioacetal of Compound 315. -

(a) A mixture of 315 (15 mg), mercuric chloride (12 mg) and mercuric oxide (9.5 mg) in 90% aqueous acetonitrile (3 ml) was refluxed under nitrogen for 30 min. T.l.c. of the reaction mixture using 5:1 ethyl acetate-ethanol as the developer showed a high R_f (0.86) charring component as well as a fluorescent, non-charring component of R_f 0.70, the latter corresponding to 2-(1,3-dithian-2-yl)uracil (314), thus indicating that glycosidic cleavage was the major reaction pathway.

(b) A mixture of 315 (25 mg), methyl iodide (0.5 ml), and barium carbonate (30 mg) in 90% aqueous acetone was heated at 55° for 4 h. T.l.c. of the reaction mixture using 9:1 benzene-ethanol as the developer showed some lower R_f material (0.10) but the major component was the free base 314 (R_f 0.25).

(c) A solution of 315 (75 mg) and benzeneseleninic anhydride⁴²² (121 mg) in anhydrous THF (10 ml) was refluxed under nitrogen for 30 min. T.l.c. of the reaction mixture showed the presence of at least five components as well as base-line material. Shortening of the reaction time or a decrease in the reaction temperature had no noticeable effect on the t.l.c. results.

2,2'-Anhydro-5,6-dihydro-6-R-methyl-5'-O-trityluridine

[318]. - A mixture of compound 310 (1 g) and freshly-activated Raney nickel (2 g) in ethanol (50 ml) was refluxed for 2 h. The nickel was removed by filtration, washed copiously with ethanol and the combined filtrate and washings evaporated under reduced pressure. The solid residue was crystallized from ethanol yielding a white powder (340 mg, 41%); m.p. 245-247°; $[\alpha]_D^{23}$ -

101.1° (ϵ 0.8, methanol); $\nu_{\text{max}}^{\text{KBr}}$ 3350 (OH), 1700 (C=O), 1570 (C=N), 1450 cm^{-1} ; n.m.r. (100 MHz, DMSO-d_6): δ 1.26 (d, 3H, J_{6,CH_3} 6.0 Hz, CH_3), 2.20 (d, 1H, $J_{5a,6}$ 4.0 Hz, H-5a), 2.28 (d, 1H, $J_{5b,6}$ 1Hz, H-5b), 2.82-3.16 (m, 2H, H-5'), 3.39 (broad s, 1H, OH, exchangeable with D_2O), 3.60-3.84 (pseudo-q, 1H, H-6), 4.15-4.28 (m, 1H, H-4'), 4.33 (broad s, 1H, H-3'), 5.11 (d, 1H, $J_{1',2'}$ 5.6 Hz, H-2'), 6.05 (d, 1H, H-1'), 7.38 (s, 15H, Ar). Irradiation of the multiplet at δ 3.60 collapsed the doublets at δ 2.20 and 1.26 to singlets.

Anal. Calc. for $\text{C}_{29}\text{H}_{28}\text{N}_2\text{O}_5$: C, 71.90; H, 5.79; N, 5.79. Found: C, 71.80; H, 5.87; N, 5.75.

5,6-Dihydro-6-(S)-(1,3-dithian-2-yl)-1- β -D-arabinofuranosyluracil (319) and 3-[(S)-1-(1,3-dithian-2-yl)]propionamido- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (320). -A solution of the tritylated anhydronucleoside 310 (2 g) in 80% aqueous acetic acid (50 ml) was refluxed for 10 min, cooled and diluted with water (50 ml). The resulting precipitate of triphenylcarbinol was filtered off and washed copiously with water. The filtrate and collected washings were then evaporated, the residual syrup dissolved in water and washed twice with ether to remove residual triphenylcarbinol. The water layer was concentrated, applied to a column (3x30 cm) of Bio-Rex 70 (H^+) cation-exchange resin and eluted with water. The first fractions yielded the detritylated nucleoside 319 (50 mg, 10%) as a solid which was recrystallized from aqueous methanol, m.p. 245-247°; R_f 0.42 (silica gel, 5:1 ethyl acetate-ethanol); $[\alpha]_D^{23} +11.4^\circ$ (ϵ 0.25, methanol); $\nu_{\text{max}}^{\text{KBr}}$ 3400 (OH), 1710 (C=O), 1690 (C=O), and 1600 cm^{-1} ; $\lambda_{\text{max}}^{\text{MeOH}}$ 245 nm (ϵ 1700); c.d. (ϵ 3.5×10^{-4} , methanol)

$\Delta\epsilon_{250} +4.80$; n.m.r. (100 MHz, DMSO- d_6): δ 1.47-2.21 (m, 2H, SCH_2CH_2), 2.59-3.01 (m, 6H, SCH_2 , H-5), 3.47-3.73 (m, 3H, H-5', H-6), 3.76-3.90 (m, 1H, H-4'), 3.93-4.15 (m, 2H, H-2', 3'), 4.76 (d, 1H, $J_{1'',6}$ 4.0 Hz, SCHS), 4.85 (t, 1H, CH_2OH , exchangeable with D_2O), 5.60 (d, 1H, CHOH , exchangeable with D_2O), 5.99 (d, 1H, $J_{1',2'}$ 5.0 Hz, H-1'), 10.31 (s, 1H, NH , exchangeable with D_2O); mass spectrum: m/e 245 (M^+ -dithiane), 133 (M^+ -base).

Anal. Calc. for $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_6\text{S}_2$: C, 42.85; H, 5.49; N, 7.69. Found: C, 42.90; H, 5.68; N, 7.78.

Further elution of the chromatography column with water gave the detritylated 2-oxazolidone derivative 320 (0.5 g, 90%) which was crystallized from aqueous methanol, m.p. 185-188°; R_f 0.23 (silica gel, 5:1 ethyl acetate-ethanol); $[\alpha]_D^{25} -32.3^\circ$ (c 0.65, methanol); $\nu_{\text{max}}^{\text{KBr}}$ 3400 (OH), 1740 (carbamate), 1680 (amide) and 1615 cm^{-1} (amide II); $\lambda_{\text{max}}^{\text{MeOH}}$ 225 (ϵ 3500), 232 (ϵ 3000) and 245 nm (ϵ 1500); c.d. (c 1.92×10^{-4} , methanol) $\Delta\epsilon_{226} +2.41$; ^1H -n.m.r. (100 MHz, DMSO- d_6): δ 1.73-2.12 (m, 2H, SCH_2CH_2), 2.55-3.19 (m, 6H, $-\text{CH}_2\text{C}=\text{O}$, SCH_2), 3.25-3.58 (m, 2H, H-5'), 3.63-3.90 (m, 1H, $-\text{CHCH}_2\text{C}=\text{O}$), 4.04 (d, 1H, $J_{1,1''}$ 10.6 Hz, SCHS), 4.15 (broad s, 1H, H-3'), 4.37-4.61 (m, 1H, H-4'), 4.68 (d, 2H, $J_{1',2'}$ 5.8 Hz, H-2'), 4.70 (t (partly buried under H-2'), 1H, CH_2OH , exchangeable with D_2O), 5.66 (d, 1H, CHOH , exchangeable with D_2O), 5.80 (d, 1H, H-1'), 6.86 (broad s, 1H, NH , exchanges slowly with D_2O), 7.51 (broad s, 1H, NH , exchanges slowly with D_2O); ^{13}C n.m.r. (D_2O): δ 177.0 (amide), 159.8 (carbamate), 90.5 (anomeric); mass spectrum; m/e 227 (M^+ -dithiane).

Anal. Calc. for $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_6\text{S}_2$: C, 42.85; H, 5.49; N, 7.69. Found: C, 42.78; H, 5.66; N, 7.87.

Acid hydrolysis of 319 to give arabinose and 5,6-dihydro-6-(S)-(1,3-dithian-2-yl)uracil (321). - A suspension of nucleoside 319 (5 mg) in 1N hydrochloric acid (1 ml) was stirred at 70° for 4 h. The reaction mixture was then cooled and the white precipitate which formed was filtered off. The precipitate was washed several times with water and shown to be the free base 321 (2 mg, 62%); m.p. 260-261°; $[\alpha]_D^{23} +22.7^\circ$ (c 0.1, methanol); $\nu_{\text{max}}^{\text{KBr}}$ 3420 (OH of tautomeric form), 3230 (NH), 1720 (broad, C=O), 1600 cm^{-1} (C=N of tautomer); $\lambda_{\text{max}}^{\text{MeOH}}$ 245 nm (ϵ 700); n.m.r. (100 MHz, DMSO- d_6): δ 1.48-2.18 (m, 2H, SCH_2CH_2), 2.58-2.98 (m, 6H, H-5, SCH_2), 3.63-3.92 (m, 1H, H-6), 4.24 (d, 1H, $J_{1',6}$ 6.0 Hz, H-1'), 7.61 (broad s, 1H, NH, exchangeable with D_2O), 10.01 (broad s, 0.5H, NH, exchangeable with D_2O).

Anal. Calc. for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_2\text{S}_2$: C, 41.38; H, 5.17; N, 12.07. Found: C, 41.38; H, 5.31; N, 12.20.

The filtrate was spotted on Whatman No. 1 paper against D-arabinose, the paper eluted in a descending manner with water-saturated 4:1 n-butanol-acetic acid and the chromatogram developed by spraying with alkaline silver nitrate solution which revealed two spots of identical R_f (0.31).

5,6-Dihydro-6-methyluracil (322). - A solution of the dithianyl compound 321 (12 mg) in N,N-dimethylformamide (1 ml) was heated for 2h at 80° in the presence of freshly-activated Raney nickel (50 mg) in ethanol (3 ml). The nickel was then removed by filtration and washed with hot N,N-dimethylformamide. Evaporation of the combined filtrate and washings left an off-white solid (5 mg, 75%) which was crystallized from methanol, m.p. 218°, (lit.³⁸⁷ 217-218°); $\nu_{\text{max}}^{\text{KBr}}$ 3200 (NH, OH), 1725 (C=O),

1695 (C=O), 1605 cm^{-1} (C=N of tautomer); n.m.r. (100 MHz, DMSO-d_6): δ 1.12 (d, 3H, J_{6,CH_3} 6.0 Hz, CH_3), 2.10-2.62 (octet (partially obscured by DMSO), approx. 2H, $J_{5a,5b}$ 16 Hz, $J_{5,6}$ 5.6 Hz, H-5), 3.50-3.68 (m, 1H, H-6), 7.52 (broad s, 1H, NH, exchangeable with D_2O), 9.96 (broad s, 1H, NH, exchangeable with D_2O).

Di-silylation of 320 to give 3-[(S)-1-(1,3-dithian-2-yl)]propionamido-3',5'-di-O-t-butyl dimethylsilyl- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (323). - A solution of the dihydroxy compound 320 (44 mg, 0.12 mmoles) and t-butyl dimethylsilyl chloride (50 mg, 0.3 mmoles) in anhydrous N,N-dimethylformamide (2 ml) and pyridine (0.5 ml) was stirred for 24 h under nitrogen. Water (0.5 ml) was then added to the reaction mixture and stirring of the solution was continued for 15 min. The solution was then evaporated to dryness under reduced pressure, the residue dissolved in chloroform (30 ml) and washed with water (2x15 ml). Drying of the chloroform solution with sodium sulfate followed by evaporation, left a syrup (97 mg) which was chromatographed on silica gel (15 g) using 1:1 benzene-ethyl acetate as developer yielding 323 as a white glass (53 mg, 75%); $[\alpha]_D^{23}$ -50.9° (c 1.4, chloroform); n.m.r. (100 MHz, CDCl_3): δ 0.04 (s, 6H, $2\times\text{CH}_3$), 0.10 (s, 3H, CH_3), 0.12 (s, 3H, CH_3), 0.88 (s, 18H, $2\times\text{t-Bu}$), 1.84-2.20 (m, 2H, SCH_2CH_2), 2.40-3.42 (m, 6H, SCH_2 , $\text{CH}_2\text{C=O}$), 3.52-3.68 (m, 2H, H-5'), 3.82-3.98 (m, 1H, NCH), 4.07 (d, 1H, $J_{1,2}$ 10 Hz, SCHS), 4.40 (broad s, 1H, H-3'), 4.49-4.60 (m, 1H, H-4'), 4.69 (d, 1H, $J_{1',2'}$ 6.0 Hz, H-2'), 5.79 (d, 1H, H-1'), 5.68-6.30 (broad d (partly buried under H-1'), 2H, NH_2 , exchangeable with D_2O);

$\nu_{\text{max}}^{\text{CHCl}_3}$ 3420 and 3540 (NH_2), 1760 (carbamate), 1695 (amide carbonyl) and 1598 cm^{-1} (amide II).

Anal. Calc. for $\text{C}_{25}\text{H}_{48}\text{N}_2\text{O}_6\text{S}_2\text{Si}_2$: C, 50.68; H, 8.11; N, 4.73; Found: C, 50.85; H, 8.08; N, 4.81.

Conversion of 319 to the oxazolidone 320. - A solution of the nucleoside 319 (20 mg) in water (1 ml) was kept at room temperature for 4 days. Evaporation of the water under reduced pressure left a solid (20 mg) identified as 320 by t.l.c. (5:1 ethyl acetate-ethanol) and n.m.r. spectroscopy.

Dehydration of 320 to give 3-[(S)-1-(1,3-dithian-2-yl)]cyanoethyl- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (328). - To a suspension of the amide 320 (43 mg, 0.12 mmoles) in anhydrous 1,4-dioxane (3 ml) and pyridine (0.08 ml, 8 eq.) at 0° was added trifluoroacetic anhydride (0.14 ml, 8 eq.). The mixture was then stirred at room temperature for 2 h by which time all starting material had dissolved. Methanol (1 ml) was added to the solution and the latter was stirred for 30 min before the solvents were evaporated in vacuo. The residual syrup was dissolved in a small quantity of water, applied to a column (11x1.5 cm) of Bio-Rex 70 (H^+) resin and eluted with water, yielding the nitrile 328 (32 mg, 77%) as a syrup which was crystallized and recrystallized from chloroform; m.p. $184-185^\circ$; $[\alpha]_{\text{D}}^{23} -40.2^\circ$ (c 0.99, methanol); $\nu_{\text{max}}^{\text{KBr}}$ 3400 (OH), 2260 ($\text{C}\equiv\text{N}$), 1740 cm^{-1} ($\text{C}=\text{O}$); n.m.r. (100 MHz, $\text{DMSO}-d_6$): δ 1.72-2.10 (m, 2H, SCH_2CH_2), 2.60-3.65 (m, 8H, SCH_2 , H-5', CH_2CN), 3.77-4.01 (m, 1H, H-4'), 3.99 (d, $J_{1,2}''$ 11.0 Hz, SCHS), 4.01 (broad s, 1H, H-3'), 4.45-4.71 (m, 1H, $-\text{CHCH}_2\text{CN}$), 4.82 (t, 1H, CH_2OH).

exchangeable with D_2O), 4.79 (dd after addition of D_2O , $J_{1',2'}$ 6.0 Hz, $J_{2',3'}$ 1.5 Hz, H-2'), 5.74 (d, 1H, -CHOH, exchangeable with D_2O), 5.86 (d, 1H, H-1').

Anal. Calc. for $C_{13}H_{18}N_2O_5S_2$: C, 45.09; H, 5.20; N, 8.09. Found: C, 44.57; H, 5.26; N, 7.91.

3-(R)-1-Methylpropionamido- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (329). - Freshly-activated Raney nickel (1.7 g) in water (5 ml) was added to a solution of the dithianyl compound 320 (314 mg) in water (10 ml) and the mixture heated at 75° for 4 h. The mixture was then filtered, the nickel washed copiously with water, the filtrate and collected washings concentrated and the residual syrup passed through a column (2.7x18 cm) of Bio-Rex 70 (H^+) cation-exchange resin (water elution) yielding 329 as a clear syrup (190 mg, 85%). The material could not be crystallized, though it was shown to be pure by paper chromatography (R_f 0.36, descending elution on Whatman No. 1 paper with water-saturated n-butanol); $[\alpha]_D^{23}$ -78.8° (c 1.1, methanol); $\nu_{\text{max}}^{\text{film}}$ 3375 (OH), 1740 (carbamate), 1670 (amide carbonyl), 1625 (amide II); n.m.r. (100 MHz, DMSO- d_6): δ 1.18 (d, 3H, J_{1,CH_3} 6.0 Hz, CH_3) 2.43 (d, 2H, $J_{1,2}$ 7.0 Hz, - $CH_2C=O$), 3.28-3.43 (octet, 2H, $J_{5'a,5'b}$ 12.0 Hz, $J_{4',5'a}$ 6.0 Hz, $J_{4',5'b}$ 7.0 Hz, H-5'), 3.80-4.14 (m, 2H, H-4', - $CHCH_3$), 4.18 (broad s, 1H, H-3'), 4.67 (d, 1H, $J_{1',2'}$ 5.0 Hz, H-2'), 4.89 (t, 1H, CH_2OH , exchangeable with D_2O), 5.62 (d, 1H, $CHOH$, exchangeable with D_2O), 5.81 (d, 1H, H-1'), 6.86 (broad s, 1H, NH , exchanges slowly with D_2O), 7.44 (broad s, 1H, NH , exchanges slowly with D_2O); mass spectrum: m/e 152 (M^+ -base).

Anal. Calc. for $C_{10}H_{16}N_2O_6 \cdot 1/2 H_2O$: C, 44.60; H, 6.32; N,

10.41. Found: C, 44.50; H, 6.30; N, 10.46.

Dehydration of 329 to give 3-(R)-1-methylcyanoethyl- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (330). - Compound 329 (41 mg) was treated with pyridine-trifluoroacetic anhydride in exactly the same manner used in the conversion of the amide 320 to the nitrile 328, yielding 330 as a syrup (23 mg, 60%); $[\alpha]_D^{23}$ -67.5° (c 1.2, methanol); $\nu_{\text{max}}^{\text{KBr}}$ 3390 (OH), 2230 (C \equiv N), 1740 cm $^{-1}$ (C=O); n.m.r. (270 MHz, DMSO-d $_6$): δ 1.35 (d, 3H, J $_{1,\text{CH}_3}$ 6.75 Hz, CH $_3$), 2.92 (octet, 2H, J $_{2a,2b}$ 15.3 Hz, J $_{1,2a}$ 7.5 Hz, J $_{1,2b}$ 6.7 Hz, CH $_2$ CN) 3.27-3.44 (m, 2H, H-5'), 3.95 (broad t, 1H, J $_{4',5'}$ 5.75 Hz, H-4'), 4.07 (q, 1H, CHCH $_3$), 4.24 (s, 1H, H-3'), 4.77 (d, 1H, J $_{1',2'}$ 5.0 Hz, H-2'), 5.03 (d, 1H, -CH $_2$ OH, exchangeable with D $_2$ O), 5.85 (d, 1H, -CHOH, exchangeable with D $_2$ O), 5.89 (d, 1H, H-1').

Anal. Calc. for C $_{10}$ H $_{14}$ N $_2$ O $_5$: C, 49.59; H, 5.79; N, 11.57. Found: C, 49.35; H, 5.55; N, 11.26.

Hydrogenation of 330 to give 3-(R)-1-methylacetamidopropyl- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (331). - A solution of compound 330 (28 mg) in anhydrous acetic anhydride (3 ml) was hydrogenated at 55 p.s.i. at room temperature for 20 h in the presence of platinum oxide (21 mg) as catalyst. The catalyst was then removed by filtration and washed copiously with methanol. The filtrate and collected washings were evaporated under reduced pressure, traces of acetic anhydride being removed azeotropically with p-xylene. The crude residue was chromatographed on silica gel using 5:1 ethyl acetate-ethanol. A minor component of R $_f$ 0.26 was first eluted and appeared to be

an inseparable syrupy mixture of the 3'-O- and 5'-O-acetyl acetamido derivatives (14 mg, 36%); $\nu_{\text{max}}^{\text{film}}$ 3320 (OH), 1750 (carbamate), 1650 (amide carbonyl), 1555 cm^{-1} (amide II); n.m.r. (270 MHz, DMSO- d_6): δ 1.80 (s, NAc), 2.02 (s, $-\text{CH}_2\text{OAc}$), 2.08 (s, CHOAc), 7.86 (broad s, NH, exchangeable with D_2O). The ratio of C-5' acetate to C-3' acetate was approximately 2:1.

Further elution of the chromatography column gave the acetamido compound 331 as a syrup (11 mg, 33%); R_f 0.16; $[\alpha]_D^{23} - 78.8^\circ$ (c 0.52, methanol); $\nu_{\text{max}}^{\text{film}}$ 3320 (OH), 1740 (carbamate), 1640 (amide carbonyl), 1560 (amide II); n.m.r. (270 MHz, DMSO- d_6): δ 1.18 (d, 3H, J_{1,CH_3} 6.0 Hz, CHCH_3), 1.72 (m, 2H, $\text{N-CH}_2\text{CH}_2$), 1.81 (s, 3H, NAc), 3.03 (t, 2H, $J_{2,3}$ 6.8 Hz, NHCH_2), 3.18-3.32 (m, 2H, H-5'), 3.70 (broad q, 1H, CH_3CH), 3.90 (broad t, 1H, H-4'), 4.22 (broad s, 1H, H-3'), 4.71 (d, 1H, $J_{1',2'}$ 5.5 Hz, H-2'), 4.96 (t, 1H, $-\text{CH}_2\text{OH}$, exchanges with D_2O), 5.67 (d, 1H, $-\text{CHOH}$, exchanges with D_2O), 5.79 (d, 1H, H-1'), 7.88 (broad s, 1H, NH, exchanges slowly with D_2O).

Anal. Calc. for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_6 \cdot 3/2 \text{H}_2\text{O}$: C, 45.71; H, 7.30; N, 8.88. Found: C, 45.80; H, 6.79; N, 8.40.

Molecular weight by mass spectrometry 288.1328. $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_6$ (M^+) requires 288.1321. The base peak was observed at 114.0890. $\text{C}_6\text{H}_{12}\text{NO}$ requires 114.0919.

Hydrogenation of a solution of compound 330 (31 mg) in anhydrous methanol (3 ml) and acetic anhydride (0.5 ml) at 55 p.s.i. at room temperature for 2 h in the presence of platinum oxide (23 mg) followed by removal of the catalyst by filtration and removal of the solvents of the filtrate by co-distillation with xylene, gave compound 331 (35 mg, 95%) with no observable

formation of O-acetates.

Attempted Detritylation of 310 to Give 2,2'-Anhydro-5,6-dihydro-6-(S)-(1,3-dithian-2-yl)uridine (332). - (a) A mixture of 310 (118 mg) and 5% palladium on charcoal (64 mg) in methanol (3 ml) was hydrogenated at 50 p.s.i. for 24 h. T.l.c. of the reaction mixture showed the presence of only starting material. The mixture was filtered and the filtrate was evaporated, leaving a residue whose n.m.r. spectrum (100 MHz, CDCl₃) indicated that it was unchanged 310.

(b) When the above procedure (a) was repeated using palladium hydroxide³⁹⁵ on carbon as the catalyst, there was again no discernible detritylation of 310 as evidenced by either t.l.c. or n.m.r. spectroscopy.

(c) To a solution of 310 (111 mg) in anhydrous THF (4 ml) and liquid ammonia (20 ml) at -78° was added lithium powder (15 mg). The solution was stirred at -78° for 30 min before ammonium chloride (275 mg) was added to destroy the lithium. The reaction mixture was then allowed to come to room temperature, nitrogen was bubbled through for 15 min and residual solvents were removed by rotary evaporation. The residual syrup was shown to consist mainly of 310 by t.l.c. and n.m.r. spectroscopy though the presence of several higher R_f impurities was also indicated.

(d) A solution of 310 (10 mg) and ferric chloride (1 mg) in anhydrous dichloromethane (2 ml) and methanol (5 μ l) was stirred for 24 h at room temperature. T.l.c. of the reaction mixture on silica gel using 9:1 benzene-ethanol as developer indicated that some detritylation had occurred as evidenced by the presence of a high R_f fluorescent component. However, at

least five other sugar components were observed on the t.l.c. plate so that this method was abandoned as a practical method of detritylation.

(e) A solution of 310 (30 mg) in anhydrous chloroform (5 ml) was added to chloroform (15 ml) saturated with HBr gas at 0°. After 5 min at 0°, t.l.c. of the reaction mixture (5:1 ethyl acetate-ethanol) showed complete detritylation accompanied by the formation of at least 4 other sugar components and much base-line material.

(f) A solution of 310 (67 mg) in 2:1 n-butanol-trifluoroacetic acid (3 ml) was stirred for 3 min at room temperature. The reaction mixture was then poured into a rapidly stirring mixture of Bexyn 201 (OH⁻) in methanol (120 ml) at 0°. After 5 min, the resin was removed by filtration and the filtrate was evaporated under reduced pressure yielding a gummy residue. Chromatography of the latter on a column (20x2.5 cm) of Bio-Rex 70 (H⁺) resin using water as the eluting solvent afforded the detritylated oxazolidone 320 (32 mg, 80%), identified by n.m.r. spectroscopy.

Detritylation of compound 318 to give 329. - A solution of compound 318 (94 mg) in 80% aqueous acetic acid (10 ml) was refluxed for 10 min, the reaction mixture cooled and the solvents evaporated under reduced pressure at room temperature. The residue was suspended in water and washed twice with ether. Evaporation of the water fraction left a syrup (50 mg) which was applied to a column (1.5 x 11 cm) of Bio-Rex 70 (H⁺) resin and eluted with water, yielding compound 329 as a clear syrup (26 mg, 52%).

3-[(S)-1-(1,3-Dithian-2-yl)]cyanoethyl-3',5'-di-O -p-nitrobenzoyl- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (333).

- To a solution of compound 320 (285 mg) in anhydrous pyridine (10 ml) was added at room temperature freshly recrystallized p-nitrobenzoyl chloride (458 mg, 3 equiv) in pyridine (5 ml). The solution was stirred for 2 h, water added (1 ml) and the mixture stirred for another hour. The solvents were then evaporated in vacuo, the residue was dissolved in chloroform (60 ml) and the latter washed successively with 4% hydrochloric acid (2 x 30 ml), saturated aqueous sodium hydrogen carbonate (2 x 30 ml) and water (3 x 30 ml). The chloroform layer was dried with sodium sulfate and evaporated, leaving a crude solid (517 mg) which was chromatographed on silica gel (30 g). Elution with 3:1 chloroform-ethyl acetate yielded the diester 333 as a solid (422 mg, 85%) after removal of solvents. Compound 333 was recrystallized from acetonitrile-water, m.p. 201-202°; $[\alpha]_D^{23}$ -42.9° (c 1.3, chloroform); n.m.r. (100 MHz, $CDCl_3$): δ 1.90-2.10 (m, 2H, SCH_2CH_2), 2.40-3.30 (m, 6H, SCH_2 , $-CH_2C=O$), 4.02-4.38 (m, 2H, $-CHCH_2C=O$, SCH_2S), 4.64 (broad s, 2H, H-4', 5'), 5.23 (d, 1H, $J_{1',2'}$ 6.0 Hz, H-2'), 5.70 (s, 1H, H-3'), 5.90 (d, 1H, H-1'), 8.25 (m, 8H, Ar); $\nu_{max}^{CHCl_3}$ 2260 (CN), 1780 (carbamate), 1740 (ester), 1615 and 1535 cm^{-1} (NO_2).

Anal. Calc. for $C_{27}H_{24}N_4O_{11}S_2$: C, 50.31; H, 3.73; N, 8.70. Found: C, 50.17; H, 3.69; N, 8.66.

Conversion of compound 333 to compound 328. - To a solution of compound 333 (190 mg) in anhydrous methanol (25 ml) and tetrahydrofuran (3 ml) was added with stirring under nitrogen a solution of 0.1N sodium in methanol (20 μ l). After one hour, the

reaction mixture was neutralized with Bio-Rex 70 (H⁺) resin, the resin was removed by filtration and the filtrate evaporated. The residue was suspended in water (30 ml) and washed with ether (3x20 ml). The water layer was then evaporated under reduced pressure leaving a solid (328, 90 mg, 88%) which was crystallized from ethanol-water, m.p. 186-186.5°; $[\alpha]_D^{24} -44.2^\circ$ (c 0.94, methanol); $\nu_{\text{max}}^{\text{KBr}}$ 3400 (OH), 2260 (C \equiv N), 1740 cm⁻¹ (C=O); n.m.r. (100 MHz, DMSO-d₆): δ 1.72-2.10 (m, 2H, SCH₂CH₂), 2.60-3.65 (m, 8H, SCH₂, H-5', CH₂CN), 3.77-4.01 (m, 1H, H-4'), 3.99 (d, J_{1,CH₃} 11.0 Hz, SCH₃), 4.01 (broad s, 1H, H-3'), 4.45-4.71 (m, 1H, -CHCH₂CN), 4.79 (dd after addition of D₂O, 1H, J_{1',2'} 6.0 Hz, J_{2',3'} 1.5 Hz, H-2'), 4.82 (t (partly buried by H-2'), 1H, CH₂OH, exchangeable with D₂O), 5.74 (d, 1H, CHOH, exchangeable with D₂O), 5.86 (d, 1H, H-1'); mass spectrum: m/e 346 (M⁺), 315 (M⁺-CH₂OH).

Anal. Calc. for C₁₃H₁₈N₂O₅S₂•H₂O: C, 42.86; H, 5.49; N, 7.69. Found: C, 42.88; H, 4.93; N, 7.52.

3-(R)-1-Methylcyanoethyl-3',5'-di-O-p-nitrobenzoyl- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (334). - To a solution of compound 329 (60 mg) in anhydrous pyridine (3 ml) was added p-nitrobenzoyl chloride (214 mg, 5 equiv) in pyridine (2 ml). The solution was stirred for 2 h by which time t.l.c. of the reaction mixture on silica gel using 2:1 benzene-ethyl acetate as developer showed consumption of all starting material and formation of a single component of R_f 0.37. Water (0.5 ml) was added to the solution and the latter stirred for another hour. The mixture was then evaporated, the residue dissolved in methylene chloride (60 ml) and successively washed with 4%

hydrochloric acid (2x30 ml), saturated aqueous sodium hydrogen carbonate (2x30 ml) and water (3x30 ml). The organic layer was dried with sodium sulfate and evaporated, leaving a yellow glass (146 mg) which was chromatographed on silica gel (15 g). Elution with 3:1 benzene-ethyl acetate gave 334 as a white glass (124 mg, 98%). A first crystallization of this glass from ethyl acetate-methylene chloride-hexane gave off-white powder, m.p. 81-82°. Recrystallization from the same solvents resulted in crystals melting at 86-87°; $[\alpha]_D^{23} -45.2^\circ$ (c 0.8, chloroform); $\nu_{\text{max}}^{\text{CHCl}_3}$ 2260 (C \equiv N), 1780 (carbamate), 1740 (ester carbonyl), 1615 and 1537 cm^{-1} (NO $_2$); n.m.r. (100 MHz, CDCl $_3$): δ 1.52 (d, 3H, J $_{1,\text{CH}_3}$ 7.0 Hz, CH $_3$), 2.56-3.04 (octet, 2H, J $_{2a,2b}$ 17.0 Hz, J $_{1,2}$ 5.8 Hz, -CH $_2$ C=O), 4.10-4.32 (pseudo-q, 1H, -CHCH $_3$), 4.46-4.70 (m, 3H, H-4', H-5'), 5.23 (d, 1H, J $_{1',2'}$ 5.5 Hz, H-2'), 5.70 (s, 1H, H-3'), 6.10 (d, 1H, J $_{1',2'}$ 5.5 Hz, H-1'), 8.30 (m, 8H, Ar). Irradiation of the quartet at δ 4.10 collapsed the octet at δ 2.56 to two doublets having J $_{\text{gem}}$ 16.0 Hz and the doublet at δ 1.52 to a singlet; mass spectrum: m/e 373.0952 (M $^{+}$ -O $_2$ NC $_6$ H $_4$ COOH).

Anal. Calc. for C $_{24}$ H $_{30}$ N $_4$ O $_{11}$: C, 53.33; H, 3.70; N, 10.37. Found: C, 53.31; H, 3.60; N, 10.06.

Conversion of compound 328 to compound 320. - A suspension of compound 328 (31 mg) in 1N sodium hydroxide (3 ml) was refluxed for 5 min by which time t.l.c. on silica gel using 5:1 ethyl acetate-ethanol as developer showed consumption of all starting material (R $_f$ 0.56) and formation of a major product of R $_f$ 0.26. After neutralization of the reaction mixture with Bio-Rex 70 (H $^{+}$) resin, the latter was removed by filtration, the filtrate evaporated under reduced pressure and the residual

syrup was applied to a column of Bio-Rex 70 (H⁺) resin and eluted with water, yielding compound 320 (12 mg, 40%) identical by n.m.r. and i.r. with that obtained from compound 310.

Unsuccessful Attempts at Hydrolysis of the Dithioacetal of 333. - (a) A mixture of 333 (7.8 mg), mercuric chloride (7 mg) and mercuric oxide (5.4 mg) in 5% aqueous acetonitrile was refluxed for 24 h under an atmosphere of nitrogen. No reaction was seen by t.l.c. of the reaction mixture (2:1 benzene-ethyl acetate).

(b) A mixture of 333 (12.3 mg), cupric chloride (5.7 mg) and cupric oxide (6.7 mg) in 99% aqueous acetone (3 ml) was refluxed for 2 h with no observable hydrolysis of starting material by t.l.c.

(c) To a solution of freshly-recrystallized N-bromosuccinimide (24.2 mg) and 2,4,6-trimethylpyridine (33 mg) in 80% aqueous acetonitrile (2 ml) was added a solution of 333 (11 mg) in acetonitrile (1 ml). After the reaction mixture had stirred for 10 min, t.l.c. showed that consumption of all starting sugar had occurred with generation of two lower R_f spots (5:1 benzene-ethanol). The solution was diluted with chloroform (6 ml) and washed successively with saturated aqueous sodium sulfite (6 ml), saturated aqueous sodium hydrogen carbonate (6 ml), 3M aqueous cupric nitrate (6 ml) and water (2x6 ml). The organic layer was dried with magnesium sulfate and evaporated, leaving a crude solid (13 mg). An n.m.r. spectrum of this mixture in deuteriochloroform did not show a low-field signal associated with the formyl proton, indicating that hydrolysis of 333 had not occurred.

(d) To a solution of 333 (12.3 mg) in 75% aqueous acetonitrile (2 ml) was added ceric ammonium nitrate (42 mg). After the solution had stirred for 5 min, t.l.c. (5:1 benzene-ethyl acetate) showed mainly base-line material which could not be raised using more polar solvents (9:1 benzene-ethanol).

3-(S)-1-Formylcyanoethyl-3',5'-di-O-p-nitrobenzoyl- β -D-arabinofurano-[1',2':4,5]-2-oxazolidone (335), (as semicarbazone 336). - A mixture of 333 (43 mg) and barium carbonate (47 mg) in dimethyl sulfoxide (4 ml) and water (0.5 ml) was heated at 55° for 15 min. The mixture was cooled before methyl iodide was added (1 ml). Heating of the mixture at 55° was resumed for 3 h after which it was cooled, diluted with acetone (20 ml) and the mixture evaporated to half volume to remove excess methyl iodide. More acetone (20 ml) was added to precipitate the barium salts, the mixture filtered, and the filtrate evaporated. The residue, dissolved in chloroform, was washed with water, the chloroform layer was dried with sodium sulfate and evaporated leaving an orange syrup (335); n.m.r. (100 MHz, DMSO- d_6): δ 9.45 (d, J 14.0 Hz, $H-C=O$). Without further purification, the foregoing syrup was dissolved in methanol (2 ml), to which was added pyridine (0.5 ml) and 0.5M aqueous semicarbazide hydrochloride (0.4 ml). The reaction mixture was evaporated, the residue dissolved in water, the latter extracted with ethyl acetate, the organic extract dried with sodium sulfate and evaporated, leaving a crude solid (41 mg) from which the semicarbazone 336 (15 mg, 37% from 333) was obtained in pure form by two recrystallizations from ethyl acetate-methanol, m.p.

192-194°; $[\alpha]_D^{23} -86.9^\circ$ (c 0.35, 9:1 methanol-ethyl acetate);
 n.m.r. (100 MHz, DMSO- d_6): δ 3.10-3.28 (m, 2H, $-\text{CH}_2\text{C}=\text{O}$), 4.40-4.60 (m, 2H, H-5'), 4.65-4.96 (m, 2H, H-4', $-\text{CHCH}_2\text{C}=\text{O}$), 5.49 (d, 1H, $J_{1',2'}$ 6.0 Hz, H-2'), 5.68 (s, 1H, H-3'), 6.10 (d, 1H, H-1'), 6.37 (broad s, 2H, NH_2 , exchangeable with D_2O), 7.23 (d, 1H, $J_{1,\text{CH}}$ 3.0 Hz, $\text{CH}=\text{N}$), 8.20-8.50 (m, 8H, Ar), 10.23 (broad s, 1H, N-NH, exchangeable with D_2O); $\nu_{\text{max}}^{\text{KBr}}$ 3450 (NH), 2270 ($\text{C}\equiv\text{N}$), 1765 (carbamate), 1735 (ester $\text{C}=\text{O}$), 1690 ($\text{NHC}=\text{O}$), 1585 ($\text{HC}=\text{N}-$), 1615 and 1535 cm^{-1} (NO_2).

Anal. Calc. for $\text{C}_{25}\text{H}_{21}\text{N}_7\text{O}_{12}$: C, 49.10; H, 3.44; N, 16.04.
 Found: C, 48.98; H, 3.30; N, 15.68.

Attempted Synthesis of 5,6-Dihydro-6-(1,3-dithian-2-yl)cytidine (337). - A solution of the unblocked 2-oxazolidone 328 (30 mg) in anhydrous methanol (20 ml) that was previously saturated with ammonia at 0° was heated for 24 h at 160° in a sealed glass tube. The reaction mixture was cooled and the solvent evaporated leaving a solid the n.m.r. spectrum of which in DMSO- d_6 indicated that it was unchanged starting material 328.

5-Bromo-2',3'-O-isopropylideneuridine (339). - A suspension of 5-bromouridine⁴⁰³ (338, 8.5 g) and cupric sulfate (35 g) in anhydrous acetone (1 l) containing concentrated sulfuric acid (1 ml) was stirred for 24 h at room temperature. The reaction mixture was filtered, the precipitate was washed with acetone (75 ml) and the filtrate was neutralized with concentrated ammonium hydroxide (0.2 ml). The solvent was evaporated under reduced pressure and the residue was dissolved in hot acetone

(200 ml). Hexane (150 ml) was added to the solution and crystallization was induced in the cold, yielding 339 as colourless needles in two crops (7.9 g, 83%); m.p. 224-227°, (lit.⁴⁰² m.p. 231-232°, ethanol-cyclohexane).

5-Bromo-2',3'-O-isopropylidene-5'-O-trityluridine (340). -

A solution of 5-bromo-2',3'-O-isopropylideneuridine (339, 7.8 g, 21.5 mmole) and freshly recrystallized chlorotriphenylmethane (6.14 g, 22 mmole) in anhydrous pyridine (150 ml) was heated at 100° for 4 h. The reaction mixture was then cooled and poured into rapidly stirring water (1200 ml). The water layer was decanted and the remaining gummy precipitate was dissolved in chloroform (1 l) and washed with water (2x250 ml). The organic layer was dried with sodium sulfate, the solvents were evaporated and the residue was crystallized from ether-hexane to give 340 as colourless needles (12.5 g, 96%), m.p. 201-202.5°; $[\alpha]_D^{23}$ -25.5° (c 1.1, chloroform); n.m.r (100 MHz, CDCl₃): δ 1.31 (s, 3H, CH₃), 1.54 (s, 3H, CH₃), 3.40 (d, 2H, J_{4',5'} 3.6 Hz, H-5'), 4.33 (q, 1H, J_{3',4'} 7.0 Hz, H-4'), 4.73 (dd, 1H, J_{2',3'} 3.0 Hz, H-3'), 4.86 (dd, 1H, J_{1',2'} 2.4 Hz, H-2'), 5.87 (d, 1H H-1'), 7.18-7.50 (m, 15H, Ar), 7.86 (s, 1H, H-6), 9.06 (broad s, 1H, NH, exchangeable with D₂O); mass spectrum: m/e 606 (M⁺ for Br⁸¹), 604 (M⁺ for Br⁷⁹).

Anal. Calc. for C₃₁H₂₉N₂O₆Br: C, 61.50; H, 4.79; N, 4.63. Found: C, 61.57; H, 4.59; N, 4.90.

Synthesis of 5,6-dihydro-6-(R)-(1,3-dithian-2-yl)-2',3'-O-isopropylidene-5'-O-trityluridine (341), 5-(S)-bromo-5,6-dihydro-6-(S)-(1,3-dithian-2-yl)-2',3'-O-isopropylidene-5'-O-

trityluridine (342) and 5-(R)-bromo-5,6-dihydro-6-(S)-(1,3-dithian-2-yl)-2',3'-O-isopropylidene-5'-O-trityluridine (343). -

A solution of nucleoside 340 (5.56 g, 9.2 mmole) in anhydrous pyridine (50 ml) was added dropwise over 45 min to a solution of the dithiane anion 126 (6.9 g, 57.6 mmole) in THF (150 ml) at -78° under nitrogen. The deep red reaction mixture was stored at -20° for 24 h. The solution was then poured into a rapidly stirred mixture of ether and saturated aqueous sodium chloride solution (800 and 100 ml, resp.), the aqueous layer was drawn off and the organic layer washed to neutrality with saturated salt solution. After drying of the organic layer with sodium sulfate and evaporation of the solvents, there remained a syrupy material which was chromatographed on silica gel (500 g) using 10:1 benzene-ethyl acetate as developer, yielding compound 342 as a foam (2.3 g, 35%) which was crystallized from methanol, m.p. $193-195^{\circ}$; R_f 0.42 (silica gel, 4:1 benzene-ethyl acetate); $[\alpha]_D^{22} -138.9^{\circ}$ (c 0.72, chloroform); $\nu_{\max}^{\text{CHCl}_3}$ 3400 (NH), 1720 cm^{-1} (carbonyl); n.m.r. (100 MHz, CDCl_3): δ 1.27 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.73-2.01 (m, 2H, $\text{SCH}_2\text{-CH}_2$), 2.49-2.65 (m, 2H, S-CH_2), 2.79-2.96 (m, 2H, S-CH_2), 3.17 (dd, 1H, $J_{4',5'a}$ 4.6 Hz, $J_{5'a,5'b}$ 9.4 Hz, H-5'a), 3.45 (t, 1H, $J_{4',5'b}$ 8.0 Hz, H-5b), 3.99 (dd, 1H, $J_{5,6}$ 1.5 Hz, $J_{2'',6}$ 4.0 Hz, H-6), 4.13-4.35 (m, 1H, H-4'), 4.63 (d (partially obscured by H-2''), 1H, $J_{3',4'}$ 6.0 Hz, H-3'), 4.69 (d, 1H, S-CH-S), 4.81 (s, 1H, H-2'), 5.07 (s, 1H, H-1'), 5.12 (d, 1H, H-5'), 7.13-7.53 (m, 15H, Ar), 7.86 (broad s, 1H, NH, exchangeable with D_2O). Irradiation of the doublet at δ 4.69 collapsed the doublet of doublets at δ 3.99 to a broad singlet. Irradiation of the multiplet at δ 4.13-4.35 collapsed

the doublet at $\delta 4.63$ to a singlet while the triplet at $\delta 3.45$ and the doublet of doublets at $\delta 3.17$ collapsed to two doublets with $J_{5a,5b} = 9.4$ Hz; mass spectrum: m/e 726 (M^+ with Br^{81}), 724 (M^+ with Br^{79}), 711 ($M^+ - CH_3$), 481 and 483 ($M^+ - trityl$).

Anal. Calc. for $C_{35}H_{37}N_2O_6S_2Br$: C, 57.93; H, 5.10; N, 3.86; Br, 11.02. Found: C, 57.59; H, 5.50; N, 3.58; Br, 10.65.

Continued elution of the chromatography column gave compound 343 as a white foam (0.66 g, 10%), which was crystallized from carbon tetrachloride-hexane, m.p. 145-150° (amorphous); R_f 0.30 (silica gel, 4:1 benzene-ethyl acetate); $[\alpha]_D^{22} +0.84^\circ$ (c 1.7, chloroform); $\nu_{max}^{CHCl_3}$ 3400 (NH), 1720 cm^{-1} (carbonyl); n.m.r. (100 MHz, $CDCl_3$): δ 1.34 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.80-2.15 (m, 2H, SCH_2CH_2), 2.76-3.03 (m, 4H, $S-CH_2$), 3.33 (d, 2H, $J_{4',5'} = 4.0$ Hz, H-5'), 4.06 (dd, 1H, $J_{2'',6} = 3.6$ Hz, $J_{5,6} = 6.0$ Hz, H-6), 3.96-4.14 (m (buried under H-6), 1H, H-4'), 4.50 (d, 1H, $S-CH-S$), 4.73 (dd, 1H, $J_{2',3'} = 6.5$ Hz, $J_{3',4'} = 5.6$ Hz, H-3'), 4.80 (d, 1H, H-5), 5.30 (dd, 1H, H-2'), 5.81 (d, 1H, H-1'), 7.16-7.54 (m, 15H, Ar), 7.65 (broad s, 1H, NH, exchangeable with D_2O). Irradiation of the doublet at $\delta 4.50$ collapsed the doublet of doublets at $\delta 4.06$ to a doublet ($J_{5,6} = 6.0$ Hz); mass spectrum: m/e 711.1027. $C_{34}H_{34}N_2O_6S_2^{81}Br$ ($M^+ - CH_3$) requires 711.1022.

Anal. Calc. for $C_{35}H_{37}N_2O_6S_2$: C, 57.93; H, 5.10; N, 3.86. Found: C, 57.59; H, 4.94; N, 3.97.

Further elution of the column with 4:1 benzene-ethyl acetate gave compound 341 as a white glass (2.2 g, 37%) which was crystallized from carbon tetrachloride-hexane, m.p. 138-139°; R_f 0.20 (silica gel, 4:1 benzene-ethyl acetate); $[\alpha]_D^{22} -$

16.7° (c 0.6, chloroform); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3410 (NH), 1710 cm^{-1} (carbonyl); n.m.r. (100 MHz, CDCl_3): δ 1.27 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.73-2.03 (m, 2H, SCH_2CH_2), 2.48-2.71 (m, 2H, H-5), 2.73-2.97 (m, 4H, SCH_2), 3.18 (dd, 1H, $J_{5'a,5'b}$ 9.4 Hz, $J_{4',5'a}$ 3.6 Hz, H-5'a), 3.46 (t, 1H, $J_{4',5'b}$ 7.4 Hz, H-5'b), 3.67-3.95 (m, 1H, H-4'), 4.11-4.27 (m, 1H, H-6), 4.61 (d, 1H, $J_{2',3'}$ 6.6 Hz, H-3'), 4.70 (d, 1H, $J_{2',6}$ 3.2 Hz, S-CH-S), 5.09 (dd, 1H, $J_{1',2'}$ 2.0 Hz, H-2'), 5.24 (d, 1H, H-1'), 7.13-7.53 (m, 15H, Ar), 8.03 (broad s, 1H, NH, exchangeable with D_2O); mass spectrum: m/e 646 (M^+), 631 ($\text{M}^+ - \text{CH}_3$), 403 ($\text{M}^+ - \text{trityl}$).

Anal. Calc. for $\text{C}_{35}\text{H}_{38}\text{N}_2\text{O}_6\text{S}_2 \cdot 3/2 \text{H}_2\text{O}$: C, 62.40; H, 6.09; N, 4.16. Found: C, 62.72; H, 5.80; N, 4.42.

Desulfurization of compound 341 to give 5,6-dihydro-2',3'-O-isopropylidene-6-(S)-methyl-5'-O-trityluridine (346). - A solution of the dithianyl compound 341 (132 mg) in ethanol (15 ml) and THF (2 ml) was refluxed for 4 h in the presence of freshly activated Raney nickel. T.l.c. of the reaction mixture on silica gel using 3:1 benzene-ethyl acetate as developer showed a major fluorescent component of R_f 0.32 contaminated with minor quantities of higher and lower R_f material. The reaction mixture was then filtered, the nickel repeatedly washed with hot ethanol and the combined filtrate and washings evaporated, leaving a crude syrup (80 mg) which was chromatographed on silica gel (15 g) using 3:1 benzene-ethyl acetate as developer. The major component (346) was thus isolated as a white foam which could not be crystallized (40 mg, 37%); $[\alpha]_{\text{D}}^{23} -32.0^\circ$ (c 0.9, chloroform); n.m.r. (100 MHz, CDCl_3): δ 1.30 (s, 3H, isopropylidene), 1.36 (d, 3H, J_{6,CH_3} 6.6 Hz CH_3

of C-6), 1.52 (s, 3H, isopropylidene), 2.32 (d, 1H, $J_{5a,5b}$ 16.6 Hz, $J_{5a,6}$ 0 Hz, H-5a), 2.80 (dd, 1H, $J_{5b,6}$ 6.0 Hz, H-5b), 3.33 (dd, 2H, $J_{4',5'a}$ 1.2 Hz, $J_{4',5'b}$ 3.2 Hz, H-5'a, H-5'b), 3.84-3.98 (broad t, 1H, H-6), 4.12-4.28 (broad q, 1H, H-4'), 4.70 (dd, 1H, $J_{2',3'}$ 4.0 Hz, $J_{3',4'}$ 6.4 Hz, H-3'), 4.96 (dd, 1H, $J_{1',2'}$ 3.0 Hz, H-2'), 5.46 (d, 1H, H-1'), 7.16-7.52 (m, 15H, Ar), 7.68 (broad s, 1H, NH, exchangeable with D_2O); mass spectrum: m/e 527 (M^+-CH_3), 2.99 ($M^+-trityl$).

Anal. Calc. for $C_{32}H_{34}N_2O_6$: C, 70.85; H, 6.27; N, 5.17.
Found: C, 70.68; H, 6.40; N, 5.10.

5,6-Dihydro-6-(R)-(1,3-dithian-2-yl)uridine (347). - A suspension of the blocked nucleoside 341 (1.3 g) in 80% aqueous acetic acid was refluxed for 30 min, the resulting solution was cooled and the solvents removed by repeated azeotropic distillation with xylene under reduced pressure. The residue was partitioned between water (100 ml) and chloroform (50 ml), the chloroform layer drawn off and the water layer was then washed with chloroform (2x40 ml). The water layer was evaporated to dryness, the resulting residue applied to a column of Bio-Rex 70 (H^+) cation exchange resin (42x2.2 cm) and the column eluted with water yielding compound 347 as a foam (425 mg, 60%) which was crystallized from methanol-ethyl acetate, m.p. 190-191°; R_f 0.29 (silica gel, 10:10:3 benzene-ethyl acetate-ethanol); $[\alpha]_D^{23}$ -46.5° (c 0.9, methanol); λ_{max}^{MeOH} 245 nm (ϵ 1700); c.d. (c 5.23×10^{-4} , methanol) $\Delta\epsilon_{250}$ -4.13; n.m.r. (100 MHz, $DMSO-d_6$); δ 1.90-2.20 (m, 2H, $S-CH_2-CH_2$), 2.66-3.00 (m, 6H, H-5, $S-CH_2$), 3.50 (broad d, 2H, $J_{4',5'}$ 3.2 Hz, H-5'), 3.71 (d, 1H, H-4'), 3.90-4.20 (m, 3H, H-2', H-3', H-6), 4.55 (d, 1H, $J_{2',6}$ 3.6 Hz,

S-CH-S), 4.84 (t, 1H, $J_{5',OH}$ 5.6 Hz, CH_2OH , exchangeable with D_2O), 5.02 (d, 1H, $CHOH$, exchangeable with D_2O), 5.25 (d, 1H, $CHOH$, exchangeable with D_2O), 5.67 (d, 1H, $J_{1',2'}$ 6.8 Hz, H-1'), 10.42 (s, 1H, NH , exchangeable with D_2O).

Anal. Calc. for $C_{13}H_{20}N_2O_6S_2$: C, 42.86; H, 5.49; N, 7.69.
Found: C, 42.62; H, 5.54; N, 7.61.

5,6-Dihydro-6-(R)-(1,3-dithian-2-yl)uracil (348). - A solution of nucleoside 347 (35 mg) in 1N hydrochloric acid (4 ml) was heated at 80° for 4 h. The reaction mixture was then cooled resulting in the formation of colourless needles which were isolated by filtration and recrystallized from methanol, yielding pure 348 (10 mg, 45%), m.p. 258.5-259°; $[\alpha]_D^{22}$ -60.4° (c 0.2, methanol); n.m.r. (100 MHz, $DMSO-d_6$): δ 1.48-2.18 (m, 2H, S- CH_2-CH_2), 2.58-2.98 (m, 6H, H-5, SCH_2), 3.63-3.92 (m, 1H, H-6), 4.24 (d, 1H, $J_{1',6}$ 6.0 Hz, H-1'), 7.58 (broad s, 1H, NH , exchangeable with D_2O), 10.08 (broad s, 1H, NH , exchangeable with D_2O).

5,6-Dihydro-6-(R,S)-formyl-2',3'-O-isopropylidene-5'-O-trityluridine (349) (as semicarbazone 350). - A mixture of nucleoside 341 (380 mg), barium carbonate (325 mg) and methyl iodide (2 ml) in 15% aqueous acetone (17 ml) was heated at 55° for 48 h. The cooled mixture was then filtered to remove the barium salts, the filtrate evaporated and the residue was dissolved in chloroform (200 ml). The chloroform solution was washed with water (3x40 ml), dried with sodium sulfate and evaporated, leaving a pale yellow syrup which, without further purification, was dissolved in methanol (10 ml) and pyridine

(0.5 ml) before addition of 0.5 M aqueous semicarbazide hydrochloride (1 ml). The solution was then heated on a steam bath for 10 min, the solvents evaporated, the residue suspended in ethyl acetate (75 ml) and washed with water (3x20 ml). The organic layer was dried with sodium sulfate and evaporated, leaving a crude syrup which was purified chromatographically on silica gel (30 g) using 9:1 benzene-ethanol as developer yielding the semicarbazone 350 (100 mg, 30% from 341) as a solid which was recrystallized twice from toluene-hexane, m.p. 160-162°; R_f 0.22 (silica gel, 9:1 benzene-ethanol); $[\alpha]_D^{23} +23.5^\circ$ (c 0.84, methanol); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3495 (NH_2), 3340 (N-NH), 3210 (CO-NH-CO), 1725 (pyrimidine C=O), 1700 ($-\text{CONH}_2$), 1640 (C=N), 1590 cm^{-1} (amide II); n.m.r. (100 MHz, CDCl_3): δ 1.30 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 2.56 (dd, 1H, $J_{5a,6}$ 6.0 Hz, $J_{5a,5b}$ 17.0 Hz, H-5a), 2.86 (d, 1H, $J_{5b,6}$ 0 Hz, H-5b), 3.33 (broad s, 2H, H-5'), 4.15 (d, 1H, $J_{3',4'}$ 3.0 Hz, H-4'), 4.47-4.86 (m, 3H, H-2', H-3', H-6), 5.99 (d, 1H, $J_{1',2'}$ 4.0 Hz, H-1'), 6.06 (broad s, 2H, NH_2 , exchangeable with D_2O), 6.98 (d, 1H, $J_{1'',6}$ 10.0 Hz, CH=N), 7.12-7.50 (m, 15H, Ar), 9.12 (broad s, 1H, NH , exchangeable with D_2O), 10.31 (broad s, 1H, NH , exchangeable with D_2O).

Anal. Calc. for $\text{C}_{33}\text{H}_{35}\text{N}_5\text{O}_7 \cdot 1/2\text{H}_2\text{O}$: C, 63.67; H, 5.79; N, 11.25. Found: C, 63.64; H, 5.68; N, 11.16.

Debromination of compound 342 to give compound 341. - A solution of compound 342 (140 mg) in ethanol (10 ml) and THF (2 ml) containing freshly activated Raney nickel was heated at 90° for 1 h. T.l.c. of the reaction mixture on silica gel using 4:1 benzene-ethyl acetate as developer showed that a single new compound of R_f 0.20 had formed. The reaction mixture was

filtered, the nickel washed repeatedly with ethanol, the combined filtrate and washings evaporated and the residual syrup chromatographed on silica gel (17 g). Elution with 4:1 benzene-ethyl acetate gave compound 341 as a foam (54 mg, 44%); $[\alpha]_D^{23} -13.0^\circ$ (c 1.0, chloroform). The i.r., n.m.r. and mass spectra of 341 obtained from 342 were identical to those of 341 obtained directly from 340.

Debromination of compound 343 to give compound 341. - When compound 343 (100 mg) was treated with Raney nickel in a manner identical to that of compound 342, compound 341 was obtained (30 mg, 33%); $[\alpha]_D^{23} -14.2^\circ$ (c 0.95, chloroform). Compound 341 obtained by this route was identical by R_f and n.m.r. as that obtained from compound 342 and compound 340.

6-Formyl-2',3'-O-isopropylidene-5'-O-trityluridine (351) and 6-formyl-2',3'-O-isopropylidene-3-methyl-5'-O-trityluridine (353) (characterized as the semicarbazones 352 and 354, respectively) from compound 342. - A mixture of compound 342 (300 mg), barium carbonate (660 mg), methyl iodide (1 ml added at 12 h intervals), and dimethyl sulfoxide (1.5 ml) in 10% aqueous acetone (17 ml) was heated at 55° under a nitrogen atmosphere for 72 h. T.l.c. of the reaction mixture on silica gel using 4:1 benzene-ethyl acetate showed complete consumption of starting material with the formation of two components of R_f 0.13 and 0.23 (compounds 351 and 353, respectively). The reaction mixture was worked-up as before (see compound 349), leaving a yellow syrup, n.m.r. (100 MHz, $CDCl_3$): δ 9.53 (s, $CH=O$). Without further purification, the aldehyde was treated

with semicarbazide hydrochloride as before (see compound 350). In this case, two semicarbazones were formed which were separated by preparative t.l.c. on silica gel using 15:1 benzene-ethanol as developer. The slower moving component was shown to be compound 352 (22 mg from 48 mg of crude 6-aldehyde, 41%) which was crystallized from ethanol-benzene-hexane, m.p. 211-212°; R_f 0.21 (silica gel, 9:1 benzene-ethanol); $[\alpha]_D^{22}$ -17.52° (c 0.51, acetone); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3540 (NH_2), 3400 (NH), 3200 (NH), 1700 (broad C=O stretch), 1580-1620 cm^{-1} (complex pattern, C=C, C=N, amide II); n.m.r. (100 MHz, $\text{DMSO}-d_6$): δ 1.04 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 2.73-3.42 (m, 2H, H-5'), 3.78-4.02 (m, 1H, H-4'), 4.48 (broad t, 1H, $J_{3',4'} 5.0$ Hz, H-3'), 5.00 (d, 1H, $J_{2',3'} 6.0$ Hz, H-2'), 5.96 (s, 2H, H-5, H-1'), 6.56 (broad s, 2H, NH_2 , exchangeable with D_2O), 7.06-7.30 (m, 15H, Ar), 7.56 (s, 1H, $-\text{CH}=\text{N}$), 10.54 (s, 1H, NH, exchangeable with D_2O), 11.20 (s, 1H, NH, exchangeable with D_2O).

Anal. Calc. for $\text{C}_{33}\text{H}_{33}\text{N}_5\text{O}_7 \cdot 1/2\text{H}_2\text{O}$: C, 63.87; H, 5.48; N, 11.29. Found: C, 63.85; H, 5.42; N, 11.19.

The faster running component (compound 354) was obtained as a solid (7 mg, 13%), m.p. 213-215°, which could not be crystallized owing to the formation of a gel in organic solvents; R_f 0.30 (silica gel, 9:1 benzene-ethanol); $[\alpha]_D^{23}$ -5.6° (c 0.23, methanol); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3540 (NH_2), 3375 (NH), 3200 (NH), 1700 (pyrimidine C=O), 1675 (amide C=O), 1620-1565 cm^{-1} (complex pattern due to C=C, C=N, amide II); n.m.r. (100 MHz, $\text{DMSO}-d_6$): δ 1.28 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.98 (s, 3H, N- CH_3), 3.00-3.54 (m (obscured by water peak), 2H, H-5'), 4.00-4.34 (m, 1H, H-4'), 4.77 (broad t, $J_{3',4'} 5.0$ Hz, H-3'), 5.24 (d, 1H, $J_{2',3'}$

6.0 Hz, H-2'), 6.26 (s, 1H, H-1'), 6.34 (s, 1H, H-5), 6.80 (broad s, 2H, NH₂, exchangeable with D₂O), 7.20-7.60 (m, 15H, Ar), 7.80 (s, 1H, CH=N), 10.82 (s, 1H, NH, exchangeable with D₂O); mass spectrum: m/e 567 (M⁺-acetone), 539 (M⁺-CH=NNHCONH₂), 415 (M⁺-base), 382 (M⁺-trityl).

Anal. Calc. for C₃₄H₃₅N₅O₇•H₂O: C, 63.45; H, 5.75; N, 10.88. Found: C, 63.87; H, 5.47; N, 10.58.

Compounds 351 and 353 (characterized as semicarbazones 352 and 354, respectively) from compound 343. - Treatment of 343 (136 mg) with methyl iodide in the same manner as described for compound 342 gave, after formation and purification of the semicarbazones, compound 352 (34 mg, 30%); m.p. 209-211°; [α]_D²³ -19.4° (c 0.9, acetone). The R_f, i.r., and n.m.r. spectra were identical to those obtained for 352 derived from 342.

Semicarbazone 354 was also isolated (6 mg, 5%), m.p. 209-214°; [α]_D²³ -4.0° (c 0.25, methanol). The R_f and n.m.r. spectrum of 354 were identical to those described previously.

6-Hydroxymethyl-2',3'-O-isopropylidene-5'-O-trityluridine (355). - To a solution of the 6-aldehyde 351 (232 mg) in ethanol (8 ml) was added dropwise a solution of sodium borohydride (20 mg) in ethanol (4 ml). The reaction mixture was stirred for 1 h at room temperature, concentrated to one-third volume under reduced pressure, diluted with ether (150 ml) and successively washed with 1N hydrochloric acid (2x20 ml), saturated aqueous sodium hydrogen carbonate (2x20 ml) and water (3x15 ml). The ether layer was then dried over sodium sulfate and evaporated to afford a clear syrup (202 mg). Boric acid complexes were removed

from this crude product by repeatedly dissolving it in methanol and evaporating it under reduced pressure. The syrup thus obtained was chromatographed on silica gel (60 g) using 1:1 benzene-ethyl acetate as developer. The component of R_f 0.21 (355) was isolated as a colourless oil which could not be crystallized (168 mg, 72%); $[\alpha]_D^{23} +14.11^\circ$ (c 0.73, chloroform); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3600-3300 (broad, OH), 3420 (NH), 1700 (C=O), 1610 cm^{-1} (weak C=C); n.m.r. (100 MHz, CDCl_3): δ 1.26 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.54 (s, 1H, OH, exchangeable with D_2O), 3.16 (dd, 1H, $J_{4',5'a}$ 4.0 Hz, $J_{5'a,5'b}$ 9.6 Hz, H-5'a), 3.44 (dd, 1H, $J_{4',5'b}$ 8.0 Hz, H-5'b), 4.22-4.38 (m, 1H, H-4'), 4.58 (s, 2H, CH_2OH , changes to doublet with J_{gem} 6.4 Hz upon addition of D_2O), 4.72 (dd, 1H, $J_{2',3'}$ 7.0 Hz, $J_{3',4'}$ 4.0 Hz, H-3'), 5.15 (d, 1H, H-2'), 5.74 (s, 1H, H-1'), 5.86 (s, 1H, H-5), 7.12-7.50 (m, 15H, Ar), 8.06 (broad s, approx. 1H, NH, exchangeable with D_2O); mass spectrum: m/e 541 (M^+-CH_3), 313 (M^+-trityl), 126 (H^+ base).

Anal. Calc. for $\text{C}_{32}\text{H}_{32}\text{N}_2\text{O}_7 \cdot 1/2\text{H}_2\text{O}$: C, 67.96; H, 5.84; N, 4.96. Found: C, 68.10; H, 5.73; N, 4.93.

6-Hydroxymethyluridine (356). - A solution of the blocked nucleoside 355 (68 mg) in 80% aqueous acetic acid (3 ml) was refluxed for 25 min, cooled and evaporated. Traces of acid were removed by azeotropic distillation with xylene at reduced pressure. The resulting crude solid was suspended in water (30 ml) and washed with chloroform (3x15 ml). The water layer was then concentrated, applied to a column of Bio-Rex 70 (H^+) cation exchange resin (30x1.65 cm) and eluted with water yielding the unblocked nucleoside 356 as a clear syrup (23 mg, 69%); $[\alpha]_D^{23}$ -

31.8° (ϵ 1.5, methanol); $\lambda_{\text{max}}^{\text{MeOH}}$ 258 nm (ϵ 6080); n.m.r. (100 MHz, DMSO- d_6): δ 3.40-3.64 (m, 2H, H-5'), 3.67-3.82 (m, 1H, H-4'), 4.02-4.21 (m, 1H, collapses to a triplet upon addition of D_2O , $J_{3',4'}$ 6.0 Hz, H-3'), 4.39 (s, 2H, CH_2 of C-6), 4.50-4.71 (m, 2H, partly exchanges with D_2O leaving dd, $J_{2',3'}$ 6.0 Hz, $J_{1',2'}$ 4.0 Hz, H-2', C-5', OH), 4.92 (d, 1H, OH, exchangeable with D_2O), 5.16 (d, 1H, exchangeable with D_2O), 5.41 (d, 1H, H-1'), 5.75 (broad s, 2H, partly exchanges with D_2O leaving a sharp singlet, H-5, CH_2OH of C-6), 11.29 (broad s, 1H, NH, exchangeable with D_2O).

Anal. Calc. for $C_{10}H_{14}N_2O_7 \cdot 1/2H_2O$: C, 42.40; H, 5.30; N, 9.89. Found: C, 42.66; H, 5.21; N, 9.75.

6-Hydroxymethyluracil (357). - A solution of nucleoside 356 (15 mg) in 1M hydrochloric acid (2 ml) was heated at 90° for 12 h, cooled and neutralized with an excess of solid barium carbonate. The undissolved salt was removed by filtration, the filtrate was evaporated to dryness and the crude residue chromatographed on a column of Bio-Rex 70 (H^+) resin which was developed with water. The first component to be eluted was ribose which was characterized by chromatography on No. 1 Whatman paper (descending elution using water-saturated n-butanol) against authentic ribose (R_f 0.17, alkaline silver nitrate detection). Continued elution of the resin column gave compound 357 as a white powder (6 mg, 76%) which was crystallized from water, m.p. 269-270° (decomp.), (lit.⁴¹⁸ m.p. 274°); n.m.r. (100 MHz, DMSO- d_6): δ 4.19 (s, 2H, CH_2), 5.50 (s, 1H, H-5), 10.60-11.04 (broad band, approx. 2H, NH, exchanges with D_2O), [lit.⁴¹⁸ n.m.r. (60 MHz, D_2O): δ 4.17 (CH_2)].

Attempted Synthesis of 6-(2,4-diketotetrahydroimidazol-5-yl)-2',3'-O-isopropylidene-5'-O-trityluridine (358). - A mixture of the crude 6-carboxaldehyde 351 (80 mg), freshly-recrystallized ammonium carbonate (56 mg), and sodium cyanide (37 mg) in methanol (10 ml) and dimethyl sulfoxide (1 ml) was stirred under 50 p.s.i. of carbon dioxide at 23° for 2 h and then at 65° for 14 h. The solution was then evaporated under reduced pressure, the residue was suspended in water (10 ml) and the mixture was brought to pH 6-7 with 1N hydrochloric acid. The water was extracted with ethyl acetate (3x10 ml) and the combined organic extracts were washed with water (10 ml). Drying of the organic layer with sodium sulfate and evaporation of the solvents left a crude orange syrup the t.l.c. (9:1 benzene-ethanol) of which showed the presence of at least six different components which were not pursued.

E- or Z-6-[(2-Carboethoxy-2-cyano)ethylidene]-2',3'-O-isopropylidene-5'-O-trityluridine (359) and E or Z-6-[(2-carboethoxy-2-cyano)ethylidene]-2',3'-O-isopropylidene-3-methyl-5'-O-trityluridine (360). - A solution of the crude carboxaldehyde mixture (351 and 353, 1.42 g), ethyl cyanoacetate (263, 3.5 ml) and ammonium acetate (20 mg) in anhydrous N,N-dimethylformamide (50 ml) was stirred at room temperature under nitrogen for 2 h. The reaction mixture was then diluted with ether (300 ml) and washed with water (3x40 ml). The ether layer was dried (magnesium sulfate) and evaporated leaving a yellow syrup which was chromatographed on silica gel (200 g) using 5:1 benzene-ethyl acetate as developer. The faster moving minor component was shown to be 360 (168 mg, 10%) and was crystallized

from ether-hexane, m.p. 104-105°; $[\alpha]_D^{23} +2.79^\circ$ (c 0.61, chloroform); R_f 0.35 (silica gel, 4:1 benzene-ethyl acetate); $\nu_{\text{max}}^{\text{CCl}_4}$ 1745 (ester C=O), 1725 (pyrimidine C=O), 1680 (pyrimidine C=O), 1630 cm^{-1} (C=C); n.m.r. (100 MHz, CDCl_3): δ 1.31 (s, 3H, CH_3), 1.44 (t, 3H, $J_{\text{CH}_2, \text{CH}_3}$ 7.2 Hz, CH_2CH_3), 1.54 (s, 3H, CH_3), 3.14 (s, 3H, N- CH_3), 3.26 (dd, 1H, $J_{4',5'a}$ 4.0 Hz, $J_{5'a,5'b}$ 10.5 Hz, H-5'a), 3.46 (t, 1H, $J_{4',5'b}$ 8.0 Hz, H-5'b), 4.25-4.50 (m, 1H, H-4'), 4.46 (q (partially obscured by H-4'), 2H, CH_2CH_3), 4.81 (dd, 1H, $J_{2',3'}$ 6.0 Hz, $J_{3',4'}$ 4.0 Hz, H-3'), 5.18 (d, 1H, H-2'), 5.44 (s, 1H, H-1'), 6.20 (s, 1H, H-5), 7.18-7.60 (m, 15H, Ar), 8.12 (s, 1H, $\text{CH}=\text{C}-\text{CN}$); mass spectrum: m/e 663 (M^+), 648 (M^+-CH_3), 420 (M^+-trityl), 415 (M^+-base).

Anal. Calc. for $\text{C}_{38}\text{H}_{37}\text{N}_3\text{O}_8 \cdot 1/2\text{H}_2\text{O}$: C, 67.85; H, 5.65; N, 6.25. Found: C, 68.21; H, 5.49; N, 6.16.

The major and slower moving component, compound 359 was isolated as a foam (0.69 g, 38%) and crystallized from ether-hexane, m.p. 122-123°; $[\alpha]_D^{23} +0.18^\circ$ (c 1.1, chloroform); R_f 0.16 (silica gel, 4:1 benzene-ethyl acetate); $\nu_{\text{max}}^{\text{CCl}_4}$ 3420 (NH), 3200 (NH), 1725 (ester C=O), 1715 (pyrimidine C=O), 1705 (pyrimidine C=O), 1635 cm^{-1} (C=C); n.m.r. (100 MHz, CDCl_3): δ 1.26 (s, 3H, CH_3), 1.38 (t, 3H, $J_{\text{CH}_2, \text{CH}_3}$ 7.0 Hz, CH_2-CH_3), 1.52 (d, 3H, CH_3), 3.22 (dd, 1H, $J_{4',5'a}$ 5.0 Hz, $J_{5'a,5'b}$ 10.0 Hz, H-5'a), 3.40 (t, 1H, $J_{4',5'b}$ 8.0 Hz, H-5'b), 4.20-4.39 (m, 1H, H-4'), 4.41 (q (partially obscured by H-4'), 2H, CH_2-CH_3), 4.71 (dd, 1H, $J_{2',3'}$ 6.8 Hz, $J_{3',4'}$ 3.6 Hz, H-3'), 5.12 (d, 1H, H-3'), 5.36 (s, 1H, H-1'), 6.08 (s, 1H, H-5), 7.14-7.54 (m, 15H, Ar), 8.05 (s, 1H, $\text{CH}=\text{C}-\text{CN}$), 8.82 (s, 1H, NH, exchangeable with D_2O); mass spectrum: m/e 649 (M^+), 635 (M^+-CH_3), 415 (M^+-base), 406 (M^+-

trityl).

Anal. Calc. for $C_{37}H_{35}N_3O_8$: C, 68.41; H, 5.39; N, 6.47.

Found: C, 67.95; H, 5.36; N, 6.19.

6-[(2-(R or S)-Carboethoxy-2-acetamidomethyl)ethyl]-2',3'-O-isopropylidene-5'-O-trityluridine (361). - A solution of the cyano derivative 359 (150 mg) in anhydrous acetic anhydride (20 ml) was hydrogenated at 50 p.s.i. at room temperature for 20 h in the presence of platinum oxide (20 mg) as catalyst. The reaction mixture was then diluted with chloroform (150 ml) and filtered through a Celite pad to remove the catalyst. The filtrate was evaporated under reduced pressure, and traces of acetic anhydride were removed by repeated azeotropic distillations with toluene. The residue was then applied to a column of silica gel (30 g), the column developed with 9:1 benzene-ethanol and the component of R_f 0.29 was isolated as a white foam (80 mg, 50%); $[\alpha]_D^{23} +2.97^\circ$ (c 0.8, chloroform); n.m.r. (100 MHz, $CDCl_3$): δ 0.92-1.28 (m, approx. 6H, CH_2CH_3 , CH_3 of isopropylidene), 1.40 (d, approx. 3H, CH_3 of isopropylidene), 1.80, 1.90, 1.95 (3s, 3H, N-Ac), 2.32-3.62 (m, approx. 7H, H-5', CH_2CHCH_2), 3.82-4.37 (m, 3H, H-4', CH_2CH_3), 4.62-4.74 (m, 1H, H-3'), 4.94-5.28 (m, 1H, H-2'), 5.64 (s, 1H, H-5), 5.70 (d, 1H, H-1'), 5.85 (broad s, 1H, NH, exchangeable with D_2O), 7.08-7.48 (m, approx. 15H, Ar), 8.10 (broad s, 1H, NH, exchangeable with D_2O); mass spectrum: m/e 697 (M^+), 682 (M^+-CH_3), 454 (M^+ -trityl). A signal was also seen at m/e 709 indicating partial saturation of the trityl group.

Anal. Calc. for $C_{39}H_{43}N_3O_9$: C, 67.14; H, 6.17; N, 6.03.

Found: C, 66.88; H, 6.47; N, 5.80.

6-[(2-(R or S)-Carboethoxy-2-acetamidomethyl)ethyl]uridine (362). - A solution of the blocked nucleoside 361 (80 mg) in 80% aqueous trifluoroacetic acid (4 ml) was stirred at room temperature for 15 min. The yellow solution was then diluted with methanol (30 ml) and toluene (100 ml) and evaporated to near dryness under reduced pressure. Azeotropic evaporation with toluene was repeated (5x30 ml) in order to remove traces of acid, yielding finally a clear syrup which was purified by chromatography on a column of Bio-Rex 70 (H⁺) resin (29x1.7 cm). Elution with water afforded the pure nucleoside derivative 362 as a syrup (34 mg, 72%); $[\alpha]_D^{23} -19.1^\circ$ (c 1.4, methanol); R_f 0.16 (silica gel, 5:1 ethyl acetate-ethanol); $\lambda_{\text{max}}^{\text{MeOH}}$ 260 nm (ϵ 12,540); c.d. (c 4.1×10^{-5} , water) $\Delta\epsilon_{260} -0.29$; n.m.r. (100 MHz, DMSO- d_6): δ 1.21 (t, 3H, J 7.0 Hz, CH_2CH_3), 1.87 (s, 3H, NHAc), 2.87 (broad s, 3H, CH_2CHCO_2), 3.23-3.89 (m, 5H, H-5', H-4', CH_2NH), 4.14 (q, 3H, CH_2CH_3 , H-3'), 4.55 (dd, 1H, J_{2',3'} 6.0 Hz, J_{1',2'} 4.0 Hz, H-2'), 4.73 (t (partially obscured by H-2'), 1H, CH_2OH , exchangeable with D_2O), 5.01 (broad s, 1H, OH , exchangeable with D_2O), 5.23 (broad s, 1H, OH , exchangeable with D_2O), 5.43 (pseudo-t, 1H, H-1'), 5.55 (s, 1H, H-5), 8.08 (d, 1H, NH-Ac , exchangeable with D_2O), 11.39 (broad s, 1H, NH of pyrimidine, exchangeable with D_2O); mass spectrum: m/e 283.1180. $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_5$ (BH⁺) requires 283.1168.

Anal. Calc. for $\text{C}_{17}\text{H}_{25}\text{N}_3\text{O}_9 \cdot \text{H}_2\text{O}$: C, 47.11; H, 6.23; N, 9.69. Found: C, 47.03; H, 6.00; N, 9.11.

6-[3-Amino-2-(R or S)-carboxypropyl]uridine (363). - A solution of compound 363 (20 mg) in concentrated aqueous barium hydroxide (2 ml) was refluxed for 6 h. The solution was cooled

and neutralized with dilute sulfuric acid. The precipitate of barium salts was removed by filtration, the filtrate was evaporated and the residue was chromatographed on a column of Bio-Rex 70 (H⁺) resin (30x2.5 cm). The column was developed with water and the ninhydrin-positive fractions were combined yielding 363 (13 mg, 56%) mainly as its barium salt; $[\alpha]_D^{23} - 25.5^\circ$ (c 0.8, water); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 260 (ϵ 7,000), 254 (ϵ 7,900), 248 nm (ϵ 7,500); c.d. (c 1.07×10^{-3} , water) $\Delta\epsilon_{255} - 0.02$; n.m.r. (80 MHz, DMSO- d_6): δ 1.20 (d, 2H, J 7.0 Hz, CH₂), 1.25 (m, 2H, CH₂NH₂, collapses to doublet upon addition of D₂O with J 9.0 Hz), 3.25-3.60 (m, 2H, H-5'), 3.85-4.25 (m, 3H (after D₂O addition), H-3', 2', 1'), 4.40 (s, 1H, H-5), 4.10-4.80 (broad band, OH, exchangeable with D₂O), 6.50, 7.15, 7.80 (s, 3H, NH, exchangeable with D₂O); mass spectrum: m/e 346 (MH⁺).

Anal. Calc. for C₁₃H₁₈O₈N₃Ba: C, 32.41; H, 3.74; N, 8.72. Found: C, 27.15; H, 5.04; N, 3.33.

When compound 363 was stirred for 10 min in water in the presence of Dowex 50W-X2 strongly-acidic cation exchange resin, no ninhydrin-positive material was recovered.

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