Tetrahedron. Vol. 33, pp. 1513 to 1518. Pergamon Press 1977. Printed in Great Britain

HETEROCYCLIC N-GLYCOSYL DERIVATIVES—XIX†

GLYCAL NUCLEOSIDES. THEIR RELATIONSHIP WITH 2',3'-UNSATURATED NUCLEOSIDES AND THEIR UTILIZATION IN THE SYNTHESIS OF 1',3'-TWO BASE NUCLEOSIDES[1]

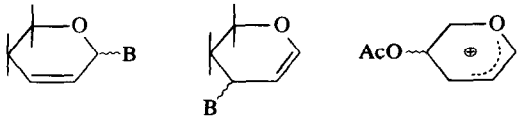
F. G. DE LAS HERAS and M. STUD
Instituto de Química Médica, Juan de la Cierva, No. 3, Madrid-6, Spain

(*Received in the UK* 19 *January* 1977; *Accepted for publication* 24 *January* 1977)

Abstract—The acid catalized reaction of tri-*O*-acetyl-D-glucal with benzotriazole or 6-methylthiopurine in acetonitrile gave a mixture of 1',2'- and 2',3'-unsaturated nucleosides, the former predominating. The relationship between these unsaturated nucleosides is studied and an allylic carbonium ion is proposed as an intermediate for these isomerizations. The acid catalized reaction of 1',2'-unsaturated nucleosides with more benzotriazole or 6-methylthiopurine gave 1',3'-two base nucleosides. The conformation and anomeric configuration of the *N*-glycosyl compounds obtained were assigned by NMR spectroscopy.

INTRODUCTION

In previous papers[2-5] we have reported the synthesis of 2',3'-unsaturated nucleosides **1** by acid catalyzed condensation of acylated glycals with purines and benzotriazoles. These 2',3'-unsaturated nucleosides under forcing reaction conditions are transformed into the 1',2'-unsaturated nucleosides **2** in which the base is attached to the C-3' of the sugar.[3,6,7] Based on this observation Ferrier and Ponpipom[6] stated that 2',3'-unsaturated nucleosides could be the kinetic controlled products and the 1',2'-unsaturated, the thermodinamic controlled ones. This rearrangement in the case of 1 - (4' - *O* - acetyl - 2',3' - dideoxy - β - D - and L - glycero - pent - 2' - enopyranosyl) benzotriazole has been shown to proceed through an allylic carbonium ion **3**,[8] the existence of which is widely accepted.[9,10]



1 **2** **3**

B = Heterocyclic base

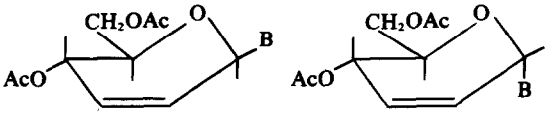
The 1',2'-unsaturated nucleosides (nucleosides with glycal-structure) **2** have been isolated by several groups[11-13] since they were initially and simultaneously reported by this and other laboratories.[3,6,7] However, no further studies have been undertaken in order to elucidate their properties or to improve the usually low yields. In this paper we report a procedure to obtain glycal nucleosides in good yields, some experiments in order to clarify their relationship with 2',3'-unsaturated nucleosides, as well as their utilization as starting materials for the synthesis of nucleosides with two *N*-heterocyclic bases attached to C-1' and C-3' of the sugar moiety, by taking advantage of the vinyl ether double bond reactivity.

†Dedicated to the memory of Prof. Dr. G. GARCÍA-MUÑOZ.

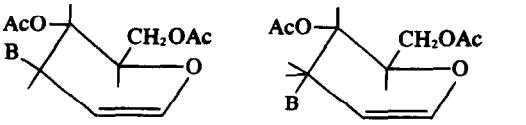
RESULTS AND DISCUSSION

The trifluoroacetic acid catalized reaction of tri-*O*-acetyl-D-glucal with benzotriazole or 6-methylthiopurine at 85–95°C for two days in acetonitrile gave good yields (90%) of 1',2'-unsaturated nucleosides **6** and **7**. A minor product was detected, the 2',3'-unsaturated-α-anomer **5**. TLC monitoring of the reaction mixture showed the initial formation of 2',3'-unsaturated nucleosides[14] **4** and **5**, which were the major products after about 16–24 h. As the reaction proceeded, the concentrations of **4** and **5** decreased, while two new products appeared, the glycal nucleoside empimers **6** and **7**. Compounds **6** and **7** became the major products after about 40–50 h. Nevertheless, the (**4**, **5**→**6**, **7**) isomerization was not complete, even in forced conditions, and depending on the base used, variable amounts of 2',3'-unsaturated nucleosides were obtained.[15]

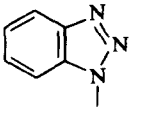
Under stronger reaction conditions (90–105°C for 2–3 days)—small amounts of the two base nucleosides **8**, **9**, **10** and **11** were also obtained.

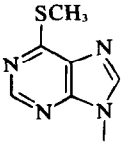


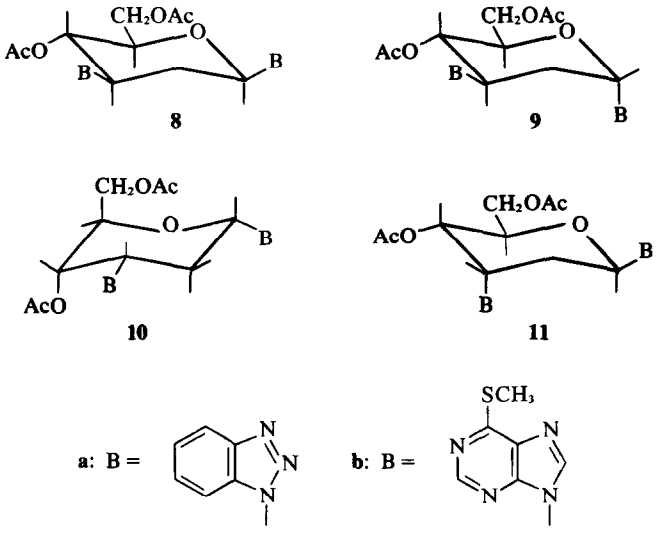
4 **5**



6 **7**

a: B = 

b: B = 

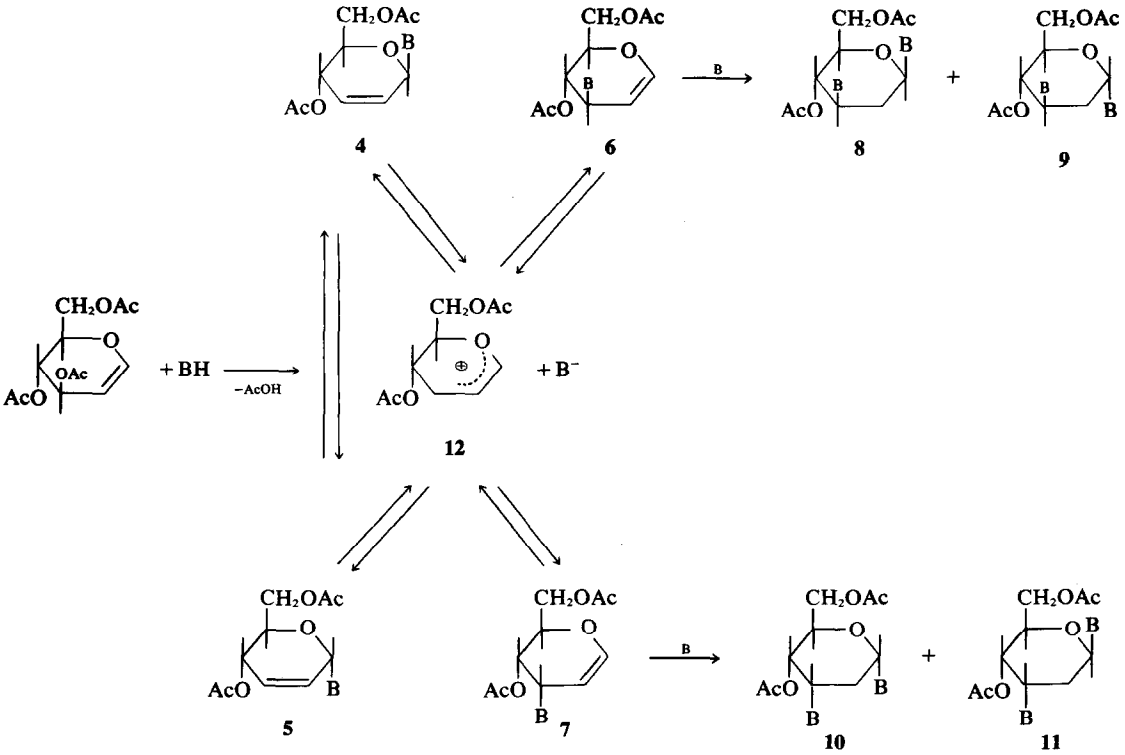


Heating in acetonitrile of any one of the unsaturated nucelosides **4**, **5**, **6** or **7** in the presence of acid yielded a mixture of the four unsaturated nucleosides isomers and small amounts of the two base nucleosides. The composition of the unsaturated nucleoside mixture was similar in all cases and did not depend on the unsaturated nucleoside used as starting material. The same treatment of **4**, **5**, **6** or **7** with an equimolecular amount of base resulted in the formation of a mixture in which double base nucleosides were the major products, minor amounts of unsaturated nucleosides, **5**, **6** and **7** were also present.

Based on these and the following observations the overall process can be represented as shown in Scheme 1. According to it, the four unsaturated nucleosides would be in equilibrium, the common intermediate being the allylic carbonium ion **12**.

As shown in Scheme 1, 2',3'-unsaturated nucleosides are initially formed by addition of the base to the glycal double bond with elimination of the acetoxy group at C-3'. This first step, which requires an acid catalyst, has been performed either in polar non protic solvents (acetonitrile, nitrobenzene,[6] nitromethane,[6]) or low polarity solvents (EtOAc,[2-5] $CHCl_3$[8]). On the other hand, the isomerization step shows a marked dependence on the nature of the solvent and the presence of an acid catalyst.

Treatment of 2',3'-unsaturated nucleosides in EtOAc or $CHCl_3$ in presence of acid, may eventually give very small amounts of glycal nucleosides, but the same treat-



Scheme 1.

ment in acetonitrile, nitromethane or nitrobenzene of either the α-anomer **5a** or the β-anomer **4a** leads to a fast isomerization giving among other products similar mixtures of unsaturated nucleosides **5a**, **6a** and **7a** in which the 1′,2′-unsaturated epimers **6a** and **7a** predominated. This transformation, 2′,3′→1′,2′ - unsaturated nucleosides, has been observed previously.[6,8]

The inverse transformation (i.e. 1′,2′→2′3′ unsaturated), the experimental verification of which is absolutely necessary for the equilibrium mechanism shown (Scheme 1), has not yet been observed. This transformation follows the same solvent and catalyst dependence pattern as before. Thus, treatment of **6a** in EtOAc with trifluoroacetic acid at 95°C for 60 h gave 62% of the unchanged starting material, and many minor products none of which was a 2′,3′-unsaturated nucleoside. However the same treatment of **6a** or **7a** in acetonitrile produced, in addition to small amounts of double base nucleosides, a mixture of unsaturated nucleosides **5a**, **6a** and **7a**.

In contrast to the 2′,3′-unsaturated nucleosides, which usually isomerize[16,17] readily, the epimerization between 1′,2′-unsaturated nucleosides requires the presence of an acid catalyst, and the presence of a polar aprotic solvent. This epimerization is never complete and is always accompanied by the formation of 2′,3′-unsaturated isomers. No reaction is observed in the absence of acid. As is shown in Scheme 1 and according to experimental facts the epimerization **6**⇄**7** should also go through the polar intermediate **12**.

This solvent and acid catalyst dependence is in better agreement with an ionic (such as **12**) or polarized intermediate rather than a sigmatropic allylic rearrangement as suggested by Ferrier and Ponpipom.[6] Their suggestion is based mainly on an observation made by these authors, that in which 2′,3′-unsaturated nucleosides yielded, by heating in nitrobenzene, the 1′,2′-unsaturated derivatives. They also obtained glycal nucleosides in other experiments, performed under different conditions but always in the presence of acid. In spite of nitrobenzene high dielectric constant (36.1 vs 38.8 for acetonitrile at 20°C) the former rearrangement seemed to be an exclusively thermal rearrangement, since no acid catalyst was added. This result disagreed with our proposed carbonium intermediate, thus, we performed a series of parallel experiments to those of Ferrier and Ponpipom. Compound **5a** was heated for 45 min in refluxing nitrobenzene giving a mixture of **4a**, **5a**, **6a** and **7a**. When a solution of **5a** in nitrobenzene was passed through a column of potassium carbonate (in order to eliminate any traces of acid from nitration of benzene) and then heated to reflux for the same time, **5a** was recovered almost unchanged. When *p*-toluenesulphonic acid was added to this acid free solution and the mixture refluxed for 15 min, isomerization appeared again. Compound **7a** was treated in the same way. Heating in nitrobenzene gave **7a** as the major product and small amounts of the other unsaturated nucleosides. Heating of a solution previously passed through a potassium carbonate column gave almost exclusively **7a**.

From these experiments one can deduce that this is not a pure thermal rearrangement, but an isomerization that requires a highly polar solvent and an acid catalyst. Further supporting evidence for the polar intermediate rather than the concerted sigmatropic allylic rearrangement is the isolation of compounds **8–11**, in addition to the expected unsaturated nucleosides, when one such unsaturated nucleoside, **4**, **5**, **6** or **7** was heated in acetonitrile with TFA. This implies that during the isomerization, the C–N bond between sugar and base moieties is broken, since the addition of a second base molecule to an unsaturated nucleoside: requires the presence of unbonded base in the reaction medium. Furthermore, the formation of double base nucleosides can be inhibited by the addition of a small amount of tri-*O*-acetyl-D-glucal, the double bond of which competes with that of the 1′,2′-unsaturated nucleoside, trapping the base as it is liberated.

On the other hand, treatment as before, of one of the unsaturated nucleosides **4a**, **5a**, **6a** or **7a** with an equimolecular amount of benzotriazole gave the four possible double base nucleosides as the major products. The latter compounds are thought to be formed by addition of the base to the glycal nucleoside double bond. When the starting materials were **6a** or **7a**, the two base nucleosides, in which the base at C-3′ had the same disposition as in the starting material, slightly predominated. Several attempts to increase this selectivity gave no significative improvements.

Reaction of **6b** with 6-methylthiopurine gave only one double base nucleoside, **8b**. This is probably due to the stability of **8b** in which all the substituents are equatorial.

The double base nucleosides are of interest because they should increase or modify the biological activities of already active bases. Conceivably, other nucleoside derivatives could be obtained by taking advantage of the glycal double bond reactivity[18] of compounds **6** and **7**. The conclusion to be drawn from the above discussion is that the reaction can be directed to the desired products by modifying the reaction conditions.

The structures of all the new compounds were based on UV and NMR spectroscopic data. In all the cases glycosylation was shown to be at N-1 for benzotriazole, and at N-9, for 6-methylthiopurine, as indicated by their UV spectra, which were within the range of the reported model compounds 1-methylbenzotriazole[19] and 9 - methyl - 6 - methylthiopurine.[20]

The magnetic parameters obtained from compounds **6** and **7** (Table 1) were very similar to those reported[5,11] for related 1′,2′-unsaturated nucleosides with bases at C-3′, thus, providing conclusive evidence of their conformations and configurations.

The assignment of the C1 conformation to both anomers **8** and **9** was made from the values of $J_{4',5'}$ 9.5–9.8 Hz which are characteristic of an axial–axial relationship for H-4′ and H-5′. The equatorial position of the base was assigned according to $J_{3',4'}$ 9.9–10.2 and $J_{2'a,3'}$ 10.8–12.5 Hz, the high value of which indicate that H-2′$_a$, H-3′ and H-4′ are axial. The anomeric configurations were based on the values of $J_{1',2'a}$ 5.0 Hz and $J_{1',2'e}$ 1.4 Hz for the α-anomer **9** and $J_{1',2'a}$ 10.9–11.0 Hz and $J_{1',2'a}$ 2.0–2.2 Hz for the β-anomers **8**.

In the case of compound **10a**, the small value of $J_{4',5'}$ 2.4 Hz indicates that these protons are in an equatorial-equatorial relationship. This, together with the observed long-range coupling between H-2′e and H-4′ (w-planar arrangement) suggest that compound **10a** exists in the 1C conformation with the acetoxymethyl group at C-5′ axial. The equatorial position for the base in C-3′ was based on the high value $J_{2'a,3'}$ 12.6 Hz characteristic of an axial–axial relationship. The α-anomeric configuration of **10** was established from the coupling constants $J_{1',2'a}$ 10.1 Hz and $J_{1',2'e}$ 3.9 Hz which indicate the axial position of H-1′.

The unusual conformation of **10a** can be better under-

Table 1. NMR parameters of 4',6' - di - *O* - acetyl - 1',2',3' - trideoxy - D - *arabino* and *ribo* - hex - 1' - enopyranos - 3' - yl derivatives ($CDCl_3$, 100 MHz)

Chemical shifts (τ values) Comp.	H-1'	H-2'	H-3'	H-4'	H-5'	H-6'	CH_3	OAc	
6a	3.26	4.56	4.16	4.39	—6.0—			8.00	8.18
6b	3.32	5.13	4.46	4.61	5.45–5.90		7.30	7.96	8.20
7a	3.10	4.81	4.15	4.58	5.31	5.63		7.90	8.36
7b	3.19	4.99	4.49	4.60	5.58–5.96		7.29	7.93	8.22

Coupling constants (Hz) Comp.	$J_{1',2'}$	$J_{1',3'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$
6a	6.1	2.1	2.0	8.6	9.0
6b	5.9	1.9	1.9	8.7	8.8
7a	6.0	1.2	5.9	5.1	10.3
7b	5.9	1.0	5.5	4.7	9.5

Table 2. NMR parameters of 1',3'-two base nucleosides **8–11** ($CDCl_3$, 100 MHz)

Chemical shifts (τ values) Comp.	Conf.	H-1'	H-2'a	H-2'e	H-3'	H-4'	H-5'	H-6'a	H-6'b	CH_3	OAc	
8a	C1	3.48	6.08	7.07	4.63	4.37		—5.7—			7.94	8.37
8b	C1	3.89	6.55	7.24	5.04	4.36	5.91	—5.75—		7.30	7.95	8.20
9a	C1	3.36	6.33	6.48	4.08	4.34	6.43	5.88	6.10		8.02	8.47
10a	1C	3.85	5.69	7.22	4.25	4.52		—5.5—		7.92		8.14
11a	C1	2.50	6.23	7.03	4.12	4.58	5.13	5.75	5.80		7.98	8.35

Coupling constants (Hz) Comp.	$J_{1',2'a}$	$J_{1',2'e}$	$J_{2'a,2'e}$	$J_{2'a,3'}$	$J_{2'e,3'}$	$J_{2'e,4'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5',6'a}$	$J_{5',6'b}$	$J_{6'a,6'b}$
8a	10.9	2.0	−13.3	12.2	4.1		9.9	9.6			
8b	11.0	2.2	−12.8	12.5	4.5		10.0	9.5			
9a	5.0	1.4	−14.2	10.8	5.8		10.2	9.8	5.0	2.1	−12.3
10a	10.1	3.9	−13.4	12.6	3.7	0.7	3.6	2.4			
11a	10.8	2.3	−14.7	5.2	2.2		4.9	10.3	5.2	1.4	−12.4

Table 3. Physical constants of compounds **6–11**

Compound	m.p. °C	$[\alpha]_D^c$	λ_{max}^{EtOH} nm		(ϵ)
6a	[a]	−71.0°	255(8040)	261(7730)sh	280(5460)
6b	149–150[b]	+61.0°	283(20,200)	290(19200)	
7a	78–79[b]	+355.0°	255(7820)	261(7500)sh	281(4830)
7b	124–125[b]	+248.0°	284(20900)	291(19550)	
8a	202–203[b]	−5.2°	254(14300)	260(13300)sh	281(8030)
8b	231–232[b]	−6.6°	285(39700)	292(40300)	
9a	[a]	+151.0°	255(15550)	261(14700)sh	281(8250)
10a	225–226[b]	+79.1°	254(14570)	260(14000)sh	279(9630)
11a	[a]	+43.6°	255(16000)	260(15000)sh	280(8450)

[a]Homogeneous syrup; [b]From EtOAc–petroleum ether; [c]Concentration ≃ 0.5 $CHCl_3$.

stood if one considers that in the alternative C1 conformation, in which the acetoxy methyl group at C-5' is equatorial, the two bases at C-1' and C-3' would both be axially oriented.

The conformation of **11a** was easily determined as C1 from the large value of $J_{4',5'}$ 10.3 Hz which establishes the *trans*-diaxial relationship between H-4' and H-5'. In addition, the observed values for $J_{3',4'}$, $J_{2'a,3'}$ and $J_{2'e,3'}$ established that the benzotriazole moiety at C-3' is axially oriented. The β-anomeric configuration was based on the high value of $J_{1',2'a}$ characteristic of axially related protons. It should be noted that H-1' and H-5' protons are strongly deshielded. The anomeric proton appeared at very low field, in the region of the aromatic benzotriazole protons. These assignations were further confirmed by double resonance experiments.

EXPERIMENTAL

M.ps are uncorrected. UV absorption spectra were recorded with a Perkin–Elmer 350 spectrophotometer. NMR spectra were recorded with a Varian XL 100 spectrophotometer, in 10–15% w/v solutions at standard probe temp., TMS being used as an internal reference. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. PLC (20 × 20 cm 2 mm thickness) was performed on PF_{254} silica gel (Merck); silica gel GF_{254} (Merck) was used for analytical TLC. Spots were visualized with UV light (254 mμ).

1 - (4,6 - *Di* - O - *acetyl* - 1,2,3 - *trideoxy* - D - arabino *and* ribo - *hex* - 1 - *enopyranos* - 3 - *yl*) *benzotriazole* **6a** *and* **7a**

A mixture of benzotriazole (1.19 g, 0.01 mole), triacetyl glucal (5.44 g, 0.02 mole), acetonitrile (60 ml) and trifluoroacetic acid (6–8 drops) was heated in a sealed tube at 85°C for 48 h. Then the solvent was evaporated *in vacuo*, and the residue dissolved in $CHCl_3$ was applied to 20 preparative TLC plates. The plates were developed 9 times with a mixture of EtOAc–petroleum ether (1:3). Under UV light two major bands were visible, which were removed and the compounds extracted with EtOAc. The slowest running band gave 1.85 g (56%) of a syrup, which was rechromatographed to pure giving the *arabino* compound **6a**. (Found: C, 58.10; H, 5.25; N, 12.50. $C_{16}H_{17}O_5N_3$ requires: C, 58.00; H, 5.17; N, 12.68%). The fastest band gave 1.15 g (34%) of the *ribo* epimer **7a** (Found: C, 57.99; H, 5.19; N, 12.40. $C_{16}H_{17}N_3O_5$ requires: C, 58.00; H, 5.17; N, 12.68%).

9 - (4,6 - *Di* - O - *acetyl* - 1,2,3 - *trideoxy* - D - arabino *and* ribo - *hex* - 1 - *enopyranos* - 3 - *yl*) - 6 - *methylthiopurine* **6b** *and* **7b**

Triacetyl-D-glucal (5.44 g, 0.02 mole) and 6-methylthiopurine (1.66 g, 0.01 mole) in acetonitrile (50 ml) containing trifluoroacetic acid (6–8 drops) were heated at 95°C for 48 h. After evaporation of the solvent, the crude thick syrup obtained was dissolved in $CHCl_3$ and applied to 22 preparative TLC plates which were eluted 5 times with EtOAc–petroleum ether (3:4), resulting in the separation of two major compounds. The slowest running band gave 1.72 g (45%) of **6b**. (Found: C, 51.08; H, 4.79; N, 15.03; S, 8.54: $C_{16}H_{18}N_4O_5S$ requires: C, 50.79; H, 4.79: N, 14.81; S, 8.45). The fastest band gave 1.66 g (44%) of pure **7b**. (Found: C, 51.04; H, 4.83; N, 15.01; S, 8.65. $C_{16}H_{18}N_4O_5S$ requires: C, 50.79; H, 4.79; N, 14.81; S, 8.45).

Preparation of benzotriazole 1',3'-two base nucleosides

(a) *From* **6a**. A mixture of 0.50 g of **6a** (1.5 mmole) and 0.18 g (1.5 mmole) of benzotriazole in 20 ml of acetonitrile with 4 drops of trifluoroacetic acid were heated in a sealed tube at 85°C for 2 days. This material was treated and chromatographed with a mixture of EtOAc–petroleum ether as before, resulting in the separation of 6 major bands.

1 - (4,6 - *Di* - O - *acetyl* - (3 - *benzotriazol* - 1 - *yl*) - 2,3 - *dideoxy* - *β* - D - arabino - *hexopyranosyl*) *benzotrialole* **8a**

The slowest band gave 0.100 g (15%) of **8a**. (Found: C, 58.37; H, 5.04; N, 18.61. $C_{22}H_{22}N_6O_5$ requires: C, 58.66; H, 4.92: N, 18.65).

1 - (4,6 - *Di* - O - *acetyl* - (3 - *benzotriazol* - 1 - *yl*) - 2,3 - *dideoxy* - *α* - D - ribo - *hexopyranosyl*) *benzotriazole* **10a**

The second running band gave 0.035 g (5%) of **10a**. (Found: C, 58.35; H, 5.07; N, 18.38. $C_{22}H_{22}N_6O_5$ requires: C, 58.66; H, 4.92; N, 18.65.

The third band in proximity to the origin gave 0.256 g (39%) of a syrup, the NMR spectra of which showed it was a 3:2 mixture of two double base nucleosides. Several attempts to separate the two components by chromatography in different solvent mixtures were unsuccessful. Their separation was accomplished by the following procedure: 0.305 g of the mixture were treated at room temp. with a mixture of methanolic sodium bicarbonate for 3 days. After filtration and evaporation of the solvent, the residue was chromatographed on 4 TLC preparative plates using a EtOAC–$CHCl_3$–petroleum ether mixture (4:4:1). Under UV light two bands were observed. The slowest moving band gave 0.068 g of deacetylated nucleoside which after acetylation with acetic anhydride-pyridine and chromatography on silica gel gave 0.078 g (12%) of pure 1 - (4,6 - *di* - *O* - *acetyl* - (3 - *benzotriazol* - 1 - *yl*) - 2,3 - *dideoxy* - *β* - D - ribo - *hexopyranosyl*)*benzotriazole* **11a** as an homogeneous syrup. (Found: C, 58.40; H, 4.68; N, 18.95. $C_{22}H_{22}N_6O_5$ requires: C, 58.66; H, 4.92; N, 18.65). From the fastest moving band were obtained 0.128 g of deacetylated nucleoside which after acetylation and chromatography as before gave 0.144 g (22%) of pure 1 - (4,6 - *di* - *O* - *acetyl* - (3 - *benzotriazol* - 1 - *yl*) - 2,3 - *dideoxy* - *α* - D - arabino - *hexopyranosyl*)*benzotriazole* **9a** as an homogeneous syrup. (Found: C, 58.60; H, 5.16; N, 18.93. $C_{22}H_{22}N_6O_5$ requires: C, 58.66; H, 4.92; N, 18.66).

The fourth running band gave 0.065 g (10%) of the starting material **6a**. The fifth band gave 0.040 g (6%) of **5a**. The sixth band gave 0.041 g of **7a**.

(b) *From* **7a**. Using the same experimental conditions the same products were obtained in the following yields. **5a** (6%), **6a** (8%), **7a** (6%), **8a** (12%), **9a** (15%), **10a** (9%), **11a** (25%).

(c) *From* **4a**. Proceeding as before the yields were **5a** (2%), **6a** (35%), **7a**(22%), **8a** (6%), **9a** (15%), **10a** (1%), **11a** (3%).

(d) *From* **5a**. The results were **5a** (7%), **6a** (38%), **7a** (24%), **8a** (5%), **9a** (7.5%), **10a** (1%), **11a** (1.5%).

(e) *From tri-O-acetyl-D-glucal and benzotriazole.* The starting materials were treated as before and gave **5a** (9.5%), **6a** (38%), **7a** (27%), **8a** (3.5%), **9a** (3.5%), **10a** (3%), **11a** (4.5%).

Isomerizations of unsaturated nucleosides

(a) *In acetonitrile.* A solution of the unsaturated nucleoside **4a**, **5a**, **6a**, or **7a** (0.01 mole) in 10 ml of acetonitrile with 3 drops TFA was heated in a sealed tube to 90–100°C for 2 days. Then, the solution was treated as before yielding after chromatography the 6 major bands already mentioned.

With **4a** as starting material a 25% yield of two base nucleosides was obtained, **5a** (1%), **6a** (35%), **7a** (22%). When starting from **5a** a 15% yield of two base nucleosides was obtained, **5a** (7%), **6a** (38%), **7a** (24%). When starting from **6a** a 28% yield of two base nucleosides was obtained, **5a** (8%), **6a** (22%), **7a** (14%). When starting from **7a** a 25% yield of two base nucleosides was obtained, **5a** (7%), **6a** (27%), **7a** (20%). In this case yields refer to the weight of the starting material. In all the other cases yields are on a molar basis.

(b) *In nitrobenzene.* A solution of 0.1 g of **5a** in 10 ml of nitrobenzene was heated to reflux for 45 min and then, the solvent was evaporated *in vacuo*. The composition of the residue, as estimated from its NMR spectrum ($CDCl_3$) was **4a** (28%), **5a** (56%), **6a** (8%), and **7a** (8%).

The same treatment of an identical solution previously passed through a small column of 5 g of K_2CO_3 gave **4a** (5%), **5a** (92%), **6a** (1%) and **7a** (2%).

To the former solution were added 5 mg of *p*-toluensulfonic acid and then heated in boiling nitrobenzene for 15 min giving **4a** (15%), **5a** (35%), **6a** (30%) and **7a** (20%).

A solution of 0.1 g of **7a** in 10 ml of nitrobenzene was heated for 6 h to reflux, after the above treatment gave **4a** (4%), **5a** (6%), **6a** (7%) and **7a** (83%).

The same treatment of an identical solution previously passed through a small column of 5 g of K_2CO_3 gave **4a** (1%), **5a** (2%), **6a** (2%) and **7a** (95%).

9 - [4',6' - *Di* - O - *acetyl* - 3' - (6 - *methylthiopurin* - 9 - *yl*) - 2',3' - *dideoxy* - *β* - D - arabino - *hexopyranosyl*] - 6 - *methylthiopurine* **8b**

A mixture of 6-methylthiopurine (0.332 g, 2 mmole) and **6b** (0.756 g, 2 mmole) was heated in acetonitrile (50 ml) with TFA (6–8 drops) at 95° for 4 days in a sealed tube. Then, the solution was treated as usual and chromatographed with EtOAc–petroleum ether (3:2). Under UV light several bands were observed. Only the four major ones were isolated and characterised. The slowest running band gave 0.227 g of **8b** (Found: C, 48.32; H, 4.28; N, 20.38; S, 12.02. $C_{22}H_{24}N_8O_5S_2$ requires: C, 48.52; H, 4.44; N, 20.58: S, 11.80%).The second running band gave 0.330 g of a mixture from which 6-methylthiopurine (0.190 g) was recovered by crystallization. The third running band gave 0.176 g of the starting material **6b**. The fastest band gave 0.097 g of **7b**.

REFERENCES

[1]Preliminary communication. G. García-Muñoz, F. G. de las Heras, R. Madroñero and M. Stud, *An. Quim.* **69**, 1335 (1973).
[2]M. Fuertes, G. García-Muñoz, R. Madroñero, M. Stud and M. Rico, *Tetrahedron* **26**, 4823 (1970).
[3]M. Fuertes, G. García-Muñoz, R. Madroñero, M. Stud and M. Rico, *Tetrahedron* **28**, 623 (1972).

[4]M. Fuertes, G. García-Muñoz, F. G. de las Heras, R. Madroñero, M. Stud and M. Rico, *Tetrahedron* **28**, 4099 (1972).
[5]G. Alonso, M. Fuertes, G. García-Muñoz, R. Madroñero and M. Stud, *J. Med. Chem.* **16**, 1056 (1973).
[6]R. J. Ferrier and M. M. Ponpipom, *J. Chem. Soc.* (C), 553 (1971).
[7]E. E. Leutzinger, R. K. Robins and L. B. Townsend, *Tetrahedron Letters* 3751 (1970).
[8]M. Fuertes, G. García-Muñoz, R. Madroñero and M. Stud, *J. Heterocyclic Chem.* **8**, 216 (1971).
[9]R. J. Ferrier, *J. Chem. Soc.* 5443 (1964).
[10]I. Lundt and C. Pedersen, *Acta Chem. Scand.* **25**, 2749 (1971).
[11]T. Kondo, H. Nakai and T. Goto, *Agr. Biol. Chem.* **35**, 1990 (1971).
[12]E. E. Leutzinger, T. Meguro, L. B. Townsend, D. A. Shuman, M. P. Schweizer, C. M. Stewart and R. K. Robins, *J. Org. Chem.* **37** 3695 (1972).
[13]T. Kondo, H. Nakai and T. Goto, *Tetrahedron* **29**, 1801 (1973).
[14]Compounds **4a** and **5a** have been described in Ref. 3, and **4b** and **5b** in Ref. 4.
[15]This reaction has also been studied with other bases such as 5,6 - dimethylbenzotriazole, 5,6 - dichlorobenzotriazole, benzimidazole, 5,6 - dimethylbenzimidazole and 5,6 - dichlorobenzimidazole. The reaction between glucal and 5,6 - dimethylbenzimidazole gave after severe reaction conditions (heating in acetonitrile in a sealed tube, at 110°C for 72 h) a mixture of **4** (25%), **5** (18%), **6** (21%) and **7** (17%). The other bases gave also mixture of 1',2'- and 2',3'-unsaturated nucleosides. F. G. de las Heras and M. Stud, unpublished results.
[16]1 - (4',6' - di - *O* - acetyl - 2',3' - dideoxy - β - D - *erythro* - hex - 2' - enopyranosyl) - 5,6 - dimethylbenzotriazole completely isomerizes to the α-anomer on standing in EtOAc solution at room temperature (see Ref. 3).
[17]R. J. Ferrier, *Topics Curr. Chem.* **14**, 389 (1970).
[18]R. J. Ferrier, *Advd. Carbohydrate Chem.* **20**, 67 (1965); *Ibid.* **24**, 199 (1969).
[19]R. H. Wiley, N. R. Smith, D. M. Johnson and J. Moffat, *J. Am. Chem. Soc.* **76** 4933 (1954).
[20]R. K. Robins, E. F. Godefroi, E. C. Taylor, L. R. Lewis and A. Jackson, *J. Am. Chem. Soc.* **83**, 2574 (1961).