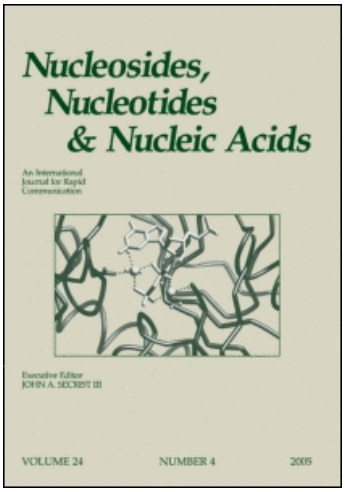

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Synthesis and Biological Evaluation of a Series of Substituted 2-Pyridine C-Nucleosides

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SYNTHESIS AND BIOLOGICAL EVALUATION OF A SERIES OF SUBSTITUTED 2-PYRIDINE C-NUCLEOSIDES.

I. Coupling reaction of organo-metallic pyridine compounds with 2,4:3,5-di-O-benzylidene-aldehydo-D-ribose.

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ABSTRACT.

Condensation of 2-lithio-pyridine and the four isomers of 2-lithio-picoline with 2,4:3,5-di-O-benzylidene-aldehydo-D-ribose, gives the D-allo- and D-altro-isomers of 2-(2,4:3,5-di-O-benzylidenepentitol-1-yl)-pyridine and the corresponding isomers of the four picoline-addition products in a good yields. On treatment with dilute hydrochloric acid or formic acid the corresponding pentitols were obtained. None of these pentitols showed an inhibitory effect on virus replication or tumor cell growth.

INTRODUCTION.

The discovery of natural C-glycosylnucleosides such as pseudo-uridine, oxazinomycin, formycin and showdomycin[1,2,3,4], together with

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the observation that some of these compounds possess antibacterial, antiviral or cytostatic activities, has led to a considerable interest in the synthesis of structurally related compounds.

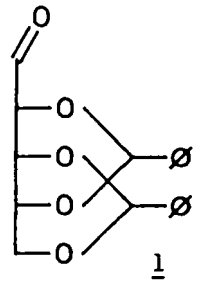
Furthermore, nicotinamide and related compounds have been shown to inhibit RNA- and DNA-viruses[5] while niacine and derivatives are known to inhibit tumor tRNA-methylase[6] and glucose phosphate isomerase[7]. It is possible that these structures owe their biological properties to the "in vivo" conversion to the corresponding nucleoside, nucleotide or NAD^+-analogue. Till now only few pyridine nucleosides (deazapyrimidine nucleosides) have been described in the literature[8,9,10,11]. Except for 1-deazauridine and 2'-deoxy-1-deazauridine synthesized by Mertes[12], all these compounds have an anomeric C_1'-N-linkage. In this paper we report the synthesis and biological evaluation of a series of pyridine C-nucleosides. Also presented are the results of the reaction of 2,4:3,5-di-O-benzylidene-aldehydo-D-ribose with the organometallic derivatives of some pyridine compounds[13], together with the acid-catalyzed conversion into the corresponding polyols. These compounds can be regarded as intermediates in the total synthesis of pyridine C-nucleosides.

RESULTS AND DISCUSSION.

Because of the sometimes vigourous reaction conditions required for cyclization reactions leading to substituted pyridine derivatives[14], the elaboration of an heterocyclic system from a suitable substituted anhydro sugar, was not considered for the moment. The results given by Mertes et al.[15] about the direct coupling of organo-metallic heterocyclic intermediates in the synthesis of C-nucleosides, prompted us to try this method for the preparation of pyridine C-nucleosides.

It has been shown by Hurd and Miles[16] that reaction of an organolithium compound with an halogen sugar prohibited selective reaction at the halogen-bearing C_1'-atom. Therefore 2,4:3,5-di-O-benzylidene-aldehydo-D-ribose 1 was chosen as the sugar synthon (Fig.1).

In earlier experiments the Grignard compounds 7 to 11 were used in an addition reaction to 1 (Scheme 1). The former compounds were synthesized by the "entrainment method", using C_2H_5MgBr as co-reactant[22,23]. The addition reactions were performed by adding dropwise a solution of 0.9 eq 2,4:3,5-di-O-benzylidene-aldehydo-D-ribose 1 in THF to the Grignard derivatives over 30 minutes.

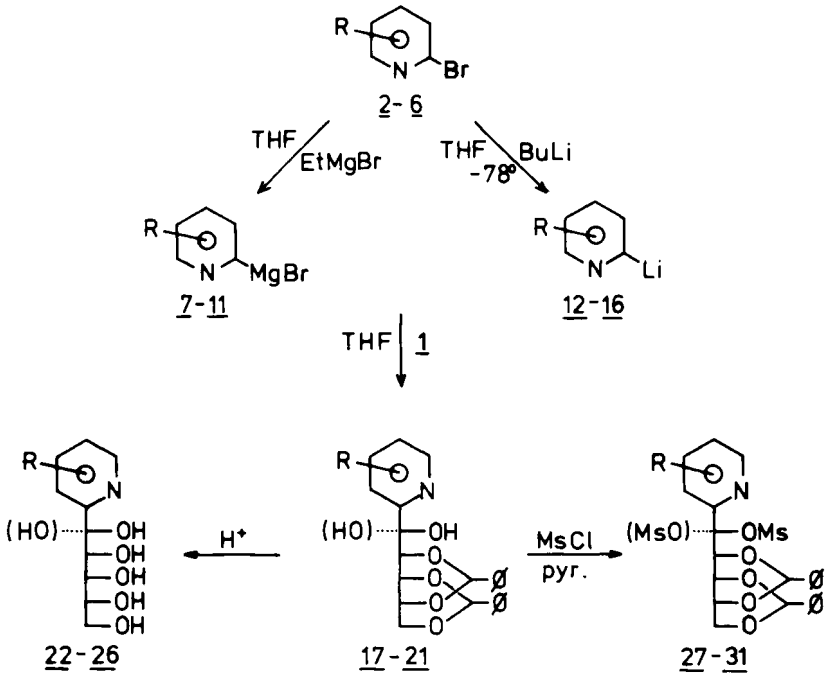


1

Fig.1

This sugar was prepared essentially according to Zinner[17,18] and Potgieter[19]. The desired picoline derivatives 3 to 6 were obtained by the "Craig-procedure" [20,21].

SCHEME 1



R=H : 2,7,12,17,22,27
R=3-Me : 3,8,13,18,23,28
R=4-Me : 4,9,14,19,24,29
R=5-Me : 5,10,15,20,25,30
R=6-Me : 6,11,16,21,26,31

The pure compounds 17 to 21 were obtained as pale yellow syrups or white foams (yields : 40-50%). However, side reactions occurred during this procedure. A substantial amount of reduced sugar and also some bipyridyl products were formed. This confirmed the observation of Nützel et al.[24] who showed that in the case of aromatic Grignard compounds bi-aromatic structures could be obtained via radical intermediates. Shortening the reaction time and decreasing the reaction temperature (T = 0°C) did not lead to higher yields since under such conditions unreacted sugar 1 was recovered. This is mainly due to the insolubility of the Grignard compounds at this lower temperature.

In order to avoid these problems organo-lithium compounds were used to achieve the couplings. The lithio-compounds 12 to 16 were prepared by a functional exchange reaction using BuLi. For the pyridine series, this reaction has been investigated extensively by Quéguiner et al.[25]. A solution of the protected sugar 1 in THF was immediately added to the lithio-compounds. The pure addition products 17 to 21 were isolated after chromatography on silica gel (yields : 17 : 77% ; 18 : 68% ; 19 : 78% ; 20 : 67% ; 21 : 84%).

To obtain the ribofuranosylderivatives, 17 was treated with HCl under different reaction conditions.

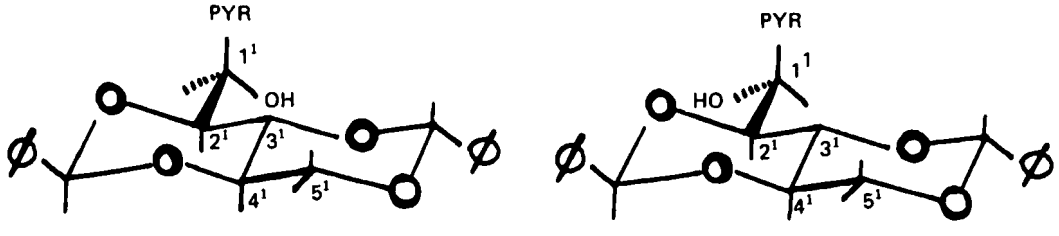
An analogous approach had been described in the synthesis of pseudouridine[26]. However in all cases the pentitol 22 was isolated and no cyclisation was observed. Probably this is due to the protonaton of the ring nitrogen atom, preventing the formation of a carbenium ion at C_1'. Such problems were also encountered by Buchanan et al.[27] during the synthesis of 3-β-D-arabinofuranosylpyrazole. Since acyclic C-nucleosides, such as the pentitols 22 to 26 could possibly have an interesting biological activity, suitable hydrolysis conditions were elaborated for obtaining these compounds in good yields. Consequently, the addition products 17 to 21 were treated with formic acid (80%) for 10 minutes at reflux temperature.

Since direct cyclisation of 17 to 21 to the corresponding ribo-furanosyl derivatives seemed impossible, a better leaving group (mesylate)[27] was introduced at C_1', by adding methanesulphonyl chloride at room temperature to a stirred solution of one of the addition products 17 to 21 in dry pyridine. The pure compounds 27 to 31 were isolated as pale yellow foams (yield 80%).

The structure of all the products was confirmed by ^{1}H-NMR and ^{13}C-NMR. The molecular weight was checked by DCI-mass spectrometry using ammonia as the reacting gas (see experimental). Optimization of the cyclisation reaction is being further investigated by a kinetic study and will be reported in a forthcoming paper. The ^{1}H-NMR spectral data (see below) show the formation of two epimeric isomers at C_1' (allo-altro forms) in nearly equal quantity for all derivatives, except for compound 18 and its further derivative 28. For the latter compounds, some side-products were formed during the coupling reaction, probably due to the prototropic properties of the 3-methyl pyridine derivative. Because of these impurities formed in compounds 18 and 28, no reliable line assignment could be given in the NMR spectra.

^{1}H-NMR DATA

Spectral data of compounds 17 to 21, 27 to 31 and 1 are given in Table 1 (except for 18 and 28). Recordings at 100 MHz show most of the protons of the sugar moiety and of the phenyl and pyridine rings as broad unresolved multiplets. The sugar protons appear in the region between 3.4 and 4.6 ppm ; the aromatic protons are located between 6.6 and 7.7 ppm. Nevertheless the structures of all compounds are well supported by the signals of H_1', H_a, H_b, H_6, the methyl protons of the pyridine substituent, or the mesylate group. The multiplicity of these peaks clearly reflects the presence of two stereoisomers shown below :



The absolute configuration at C_2', C_3' and C_4' corresponding to the D-ribose configuration, can only be converted into a transannelated bicyclic form. The phenyl groups are assumed to occur only in the equatorial position. So the only stereoisomerism can be obtained by epimeric forms at C_1', formed in the addition reaction to the original aldehyde group. Hence diastereotopic differentiation in the spectra can be observed especially in the H_a and H_b protons of the rigid ring system, also

TABLE 1 ^{1}H-N.M.R-chemical shifts of 1, 17, 18, 19, 20, 21, 27, 29, 30, 31.(1)

	H_1'	H_a H_b	$H_{2',3',4',5',5''}$	CH_3
1		5.60(s) 5.71(s)	3.85-4.45(m)	
17	5.18(br.d)	5.50(s) 5.61(s) 5.68(s) 5.75(s)	3.9-4.5(m)	--
18	5.20(d) 5.24(s)	5.56(s) 5.68(s)	3.9-4.5(m)	2.32(s) 2.35(s)
19	5.08(br.d)	5.42(s) 5.59(s) 5.63(s) 5.70(s)	3.9-4.45(m)	2.27(s) 2.30(s)
20	5.17(br.d)	5.48(s) 5.62(s) 5.68(s) 5.76(s)	3.9-4.45(m)	2.30(s)
21	5.13(br.d)	5.51(s) 5.64(s) 5.72(s) 5.80(s)	3.9-4.5(m)	2.50(s)

	H_1'	H_2'[a]	H_6	H_a H_b	CH_3	CH_3SO_2-
27	6.04(m)	4.90(br.d)	8.62(d)	5.46(s) 5.68(s) 5.86(s)		3.00(s) 3.04(s)
29	5.88(d)	4.90(br.d)	8.38(d)	5.72(s) 5.56(s) 5.46(s)	2.28(s) 2.20(s)	2.88(s) 2.96(s)
30	5.94(d)	4.80(br.d)	8.34(br.s)	5.72(s) 5.56(s) 5.48(s)	2.28(s) 2.31(s)	2.88(s) 2.93(s)
31	5.90(m)	4.74(br.d)	----	5.74(s) 5.54(s) 5.50(s) 5.46(s)	2.47(s) 2.49(s)	2.88(s) 2.93(s)

(1):Obtained at 100 Mhz from $CDCl_3$-solutions using TMS as internal standard.

good resolution is found in the methylprotons of both mesylate group and pyridine substituent. The latter signals are most appropriate to measure the epimeric ratio.

^{13}C-NMR DATA

The aromatic part of the ^{13}C-NMR spectra consists of both the pyridine and the benzylidene carbon signals.The peaks due to the phenyl carbon atoms (125.9 ; 127.7 ; 128.8 ; 137.2 ppm) could be sorted out and assigned by comparison with the spectrum of 2,4:3,5-di-O-benzylidene-aldehydo-D-ribose 1 which contained no other aromatic carbons. The assignment of the pyridine signals, achieved by using chemical shift arguments in product 17 (C_2 : 158.93, 158.95 ; C_3 : 120.72, 121.16 ; C_4 : 136.21, 136.41 ; C_5 : 122.12, 122.33 ; C_6 : 148.01, 148.16 ppm) were confirmed for the products 18 to 21 by the observed substituent shift increments on introduction of the methyl group at the different ring positions. All the pyridine signals appeared as doublets resulting from the allo-altro-epimers, with the greatest splitting for C_2 (0.8 ppm) and C_3 (0.4 ppm). The benzylidene and pyridine signals appear at almost identical values for the mesylates 27 to 31 and for the corresponding addition products 17 to 21. The assignment of the sugar signals was not straightforward but could be achieved for the mesylates 27 to 31 because of the following observations :

- The signal at ca 68 ppm is the only methylene group in this region as was proved by an INEPT-type of experiment in which CH_2-groups appear with a negative intensity.
- Selective proton decoupling at 6.1 and 4.9 ppm enables the identification of C_8 and C_9 in 27.
- Irradiation of protons at 4.0 ppm gives a decoupling of both the signals at 72.7 and 73.8 ppm. The former signal, being unchanged by mesylation (comparing to 17) is identified as C_{11}, leaving the latter signal for C_{10}.

The assignment of the carbohydrate carbon atoms of compounds 17 to 21 was obtained according to following reasons :

- Spectra of 20 recorded with variable concentrations of $Eu(fod)_3$ in CCl_4 gave the largest Lanthanide Induced Shift (LIS) for the signals at 73.5, *ca.* 81 and 70.1 ppm in decreasing order of magnitude. Complexation is expected to take place at the C_8 - OH-group eventually in combination with the pyridine nitrogen atom.

The signal at 73.5 ppm is therefore assigned to C_8, which correlates with a strong deshielding on mesylation.

- The signal at 72.5 ppm is attributed to C_{11} because of its very low LIS-value and the absence of mesylation shift.
- C_9 and C_{10} are differentiated for chemical shift reasons.

For the ^{13}C-NMR spectra of the aliphatic C-nucleoside analogues, the assignment of the pyridine carbon atoms in 22, which is straightforward, can be used in combination with pyridine methyl substitution increments for the other analogues. All the carbohydrate carbon atoms give a narrow group of peaks in the region 71.6 to 75.2 ppm. It is therefore impossible to identify them separately. The ^{13}C-NMR shift data are gathered in Table 2.

BIOLOGICAL STUDIES

The pentitols 22 to 26 were evaluated for both antiviral and antitumor activity.

- Inhibition of virus-induced cytopathogenicity.

Confluent PRK (Primary Rabit Kidney) cell cultures in Falcon microtiter trays were inoculated with 100 $CCID_{50}$ of virus, 1 $CCID_{50}$ being the virus dose required to infect 50% of the cell cultures. After 1 hour of virus adsorption, residual virus was removed and the cell cultures were incubated in the presence of varying concentrations (400, 200, 100, ... µg/ml) of the test compounds. Viral cytopathogenicity was recorded as soon as it reached completion in the control virus infected cell cultures. As shown in Table 6, none of the test compounds (22 - 26) proved active in inhibiting virus replication.

- Inhibition of tumor cell growth.

Murine leukemia L1210 cells and murine mammary carcinoma FM3A cells were seeded in microtiter trays at 5×10^4 cells per well and human lymphoblast Raji cells at 7.5×10^4 cells per well, in the presence of varying concentrations (1000, 100, 10, ... µg/ml) of the test compounds. The cells were allowed to proliferate for 48 hrs (72 hrs for Raji cells) at 37°C in a humidified, CO_2-controlled atmosphere. The growth of the cells was linear during this incubation period. At the end of the

TABLE 2: ^{13}C-N.M.R.-chemical shifts of 17,19,20,21,22,23,24,25,26,27,29,30,31.(1)

	C_2	C_3	C_4	C_5	C_6	C_7	CH_3SO_2
22	160.68 159.56	C_5	139.19	124.47 124.08 123.80 122.72	148.60		
23	157.03	132.22	140.51	124.13	146.35	17.93	
24	159.17 157.17	C_5		126.91 126.27 125.14		22.17	
25	156.10 154.79	124.47 123.35	143.28 143.18	136.36 136.07	145.42	18.08	
26	158.14 156.74	122.28 121.30	143.48 143.62	126.06 125.69	156.10	21.29	

(1): Obtained from $CDCl_3$-solutions, using the solvent signal as internal standard, except for 22 to 26 which are obtained from D_2O-solutions using 1,4-dioxane as reference.

	C_7	C_8	C_9	C_{10}	C_{11}	C_{12}	CH_3SO_2
27		82.56 80.03	79.34 78.95	73.84	72.76 72.61	68.62	38.64 38.50
29	21.00	82.75 80.26	79.34 78.80	73.78	72.61 72.41	68.57	38.50 38.30
30	17.93	82.31 80.31	79.09 78.70	73.73 73.58	72.42	68.37	38.45 38.25
31	24.12	82.60 80.07	79.09 78.70	73.64	72.47 72.37	68.42	38.45 38.30
17		73.88 73.73	81.29 80.65	70.45	72.86 72.47	68.71	
19	21.05	73.98 73.84	81.44 80.81	70.52	73.10 72.91	68.77	
20	16.62	73.50 73.11	81.15 80.37	70.13	72.33 72.03	67.94	
21	24.22	74.13 73.88	81.68 80.86	70.38	72.91 72.57	68.77	

TABLE 3 : Biological evaluation for antiviral and antitumor activity

Compound	Minimal inhibitory concentration[1] (µg/ml)					
	Herpes simplex virus type 1	Herpes simplex virus type 2	Vaccinia virus	Vesicular stomatitis virus	L1210 cells	FM3A cells
22 to 26	>400	>400	>400	>400	>1000	>1000
	Raji cells	Hepatoma cells				
22 to 26	>1000	>1000				

(1) Required to reduce virus-induced cytopathogenicity or tumor cell growth by 50%.

incubation period, the cells were counted in a Coulter Counter (Coulter Electronics Harpenden Herts, England). Rat Novikoff Hepatoma cells were seeded in microtiter trays at 1.25×10^4 cells per well in the presence of varying concentrations of the test compounds. After 2 days, the medium was discarded and replaced by fresh medium. After incubation for another day the cells were trypsinized and counted in a Coulter counter. As shown in Table 3, none of the test compounds (22 - 26) proved active in inhibiting the growth of tumor cells.

EXPERIMENTAL

1. Materials and methods :
   - 2-Bromopyridine, 2-amino-3-methylpyridine, 2-amino-4-methylpyridine, 2-amino-5-methylpyridine, 2-amino-6-methylpyridine, n.-butyllithium (1.6 M in n.-hexane) and D-ribose were purchased from Aldrich Chemicals.
   - THF was distilled from $LiAlH_4$ and stored over sodium-wire.
   - All reactions involving organometallic compounds were performed under dry N_2-atmosphere.

- The concentration of n.-C_4H_9Li in hexane was estimated from a GC-analysis of the reaction products of an aliquot of the standard solution with benzaldehyde using undecane as internal standard.
- Melting points were taken on a Melt-Temp unit.
- ^{1}H-NMR spectra were recorded on a 100 MHz JEOL JNM-PS 100 apparatus, the ^{13}C-NMR spectra on a JEOL FX-100 connected to a TI-980B computer system.
- D/CI-mass spectra were run on a RIBERMAG 10-10 (NERMAG S.A.) quadrupole mass spectrometer equiped with a SIDAR data system. Primary ionization of the reagent gas (NH_3) was performed by 70 eV electrons using an emission current of 80 mA. The ion source pressure was around 0.3 Torr.

2. Synthesis :

2-Bromo-3-methyl-pyridine (3) :

The 2-bromopicolines were prepared from the corresponding 2-amino-picolines by using the method of Craig.

In an externally cooled 3-necked flask equipped with stirrer, thermometer and dropping funnel, 2-amino-3-methylpyridine (12 g = 0.11 mol) was dissolved at -5°C in a well stirred solution of 48% hydrobromic acid (70 ml).

Keeping the temperature below 0°C, 17 ml of bromine (2.125 mol) was added.

A solution of 21 g (1.9 mol) of sodium nitrite in 30 ml of H_2O was then gradually added, keeping the temperature below 5°C until near the end of the reaction when the reaction temperature rose spontaneously to 10°C.

A solution of 45 g of sodium hydroxide in 115 ml of H_2O was then added dropwise.

The resulting oil was extracted with ether and distilled in vacuo.

Redistillation yielded the pure product.

Products 4, 5 and 6 were prepared in the same way, except for 2-bromo-5-methylpyridine which was recrystallized from petroleum ether.

Yields : 3 : 45% ; 4 : 77% ; 5 : 58% ; 6 : 70%.

3 : bp.218-219°C (76-77 °C/7 mm) ;

4 : bp.223-225°C (100-105 °C/8 mm) ;

5 : mp.46°C ;

6 : bp.199-200°C (80 °C/15 mm).

2,4:3,5-di-O-Benzylidene-aldehydo-D-ribose 1

The hydrated sugar was prepared essentially according to Zinner[17,18] and Potgieter[19] and was dried in vacuo at 100°C for 3 hrs prior to use.

D-allo- and D-altro-isomers of 2-(2,4:3,5-di-O-benzylidenepentitol-1-yl)-pyridine 17 and the corresponding picoline addition products 18 to 21.

---

a. With the Grignard reagents (7 to 11) :

9.6 g (0.4 mol) of dry magnesium turnings and 20 ml of absolute diethylether were placed in a 3-necked flask equipped with stirrer, N_2-inlet tube, dropping funnel and reflux watercondenser. A solution of ethyl bromide (3 g) in ether (10 ml) was added dropwise. A cristal of iodine was added to initiate the reaction. When the solution was boiling, the stirrer was started and a solution of pure, dry 2-bromo-pyridine (16 g = 0.1 mol) and ethyl bromide (30 g = 0.27 mol) in 80 ml of ether was slowly added at such a rate that the solution continued to boil gently. The formation of the Grignard reagent was then completed by refluxing the mixture for another two hours.

The four picoline-(2)-magnesium bromide derivatives 8 to 11 were made in the same way.

To the solutions described above, a solution of 2,4:3,5-di-O-benzylidene-aldehydo-D-ribose (0.9 eq) in dry THF was slowly added over 30 minutes and the mixture was refluxed for 2 hrs. Then, slowly, 50 ml of H_2O was added. Extraction with $CHCl_3$ (3 x 50 ml), drying on $MgSO_4$ and evaporation left a brown syrup which was chromatographed on silica gel with ethyl acetate/ hexane (30:70). The pure products were obtained as pale yellow syrups or white foams. Yields : 40-50%.

b. With the lithio compounds (12 to 16) :

In a 3-necked flask equipped with a magnetic stirrer, a N_2-inlet tube, a dropping funnel and a $CaCl_2$-tube was put 2-bromo-pyridine 2

(431 mg = 2.73 mmol) or 2-bromo-picoline 3, 4, 5 or 6 (470 mg = 2.73 mmol) and 15 ml of $LiAlH_4$ distilled tetrahydrofuran.

The flask was cooled at -78°C in an acetone/dry ice bath and the solution was stirred for 15 minutes. Then butyl-lithium, precooled at -20°C (1.71 ml ; 1.6 M in hexane = 2.736 mmol) was added in two parts while stirring, avoiding a rise of temperature above -60°C.

The solution became red. The stirring was continued for 10 minutes.

To the red solutions described above, a solution of 2,4:3,5-di-O-benzylidene-aldehydo-D-ribose (740 mg = 2.27 mmol) and dry THF (20 ml) was slowly added over 30 minutes, keeping the temperature at -78°C. The solutions turned pale yellow. The mixtures were then allowed to warm up overnight to room temperature.

Water (50 ml) and methanol (20 ml) were added slowly to the solutions and the mixtures were extracted several times with chloroform. The combined chloroform extracts were dried on $MgSO_4$ and evaporated, leaving pale yellow syrups.

These syrups were heated for 3 hours in vacuo at 100°C to remove the unreacted 2-bromopyridine or 2-bromopicolines.

The syrups were chromatographed on a silica gel column using ethyl acetate/hexane (30/70). The allo- and altro-isomers were not separated. The pure products were obtained as pale yellow syrups or white foams. Yields : 17 : 77% ; 18 : 68% ; 19 : 78% ; 20 : 67% ; 21 : 84%. DCI-data : 17 : MH^+ : 406 (100) ; 18 to 21 : MH^+ : 420 (100).

D-Allo- and D-altro-2-(pentitol-1-yl)-pyridine 22 and D-allo- and D-altro-2-(pentitol-1-yl)-3(or 4,5,6)-methylpyridine 23, 24, 25 and 26.

A solution of 17 (or 18 to 21) (1.2 mmol) in 80% formic acid (20 ml) was heated at 100°C for 10 minutes. After cooling the solution was extracted with chloroform (2 x 30 ml) to remove all benzaldehyde formed. Then the solution was evaporated in vacuo to remove the formic acid.

20 ml of distilled water was added and the solution was made neutral by adding dilute ammonia.

Extraction with chloroform, followed by evaporation in vacuo of the water layer, left a white solid product, mainly ammonium formate. Most of the ammonium formate was removed by lyophilisation.

The allo-altro mixture was purified by reverse phase chromatography (RP8) using water/methanol (80/20). The solvent was removed under reduced pressure and the products were obtained as heavy syrups. Yield : 75-80%.

DCI-data : 22 : MH^+ : 230 (100) ; 23 to 26 : MH^+ : 244 (100).

solutions and the mixtures were extracted several times with chloroform. The combined chloroform extracts were dried on $MgSO_4$ and evaporated, leaving pale yellow syrups.

These syrups were heated for 3 hours in vacuo at 100°C to remove the unreacted 2-bromopyridine or 2-bromopicolines.

The syrups were chromatographed on a silica gel column using ethyl acetate/hexane (30/70). The allo- and altro-isomers were not separated. The pure products were obtained as pale yellow syrups or white foams. Yields : 17 : 77% ; 18 : 68% ; 19 : 78% ; 20 : 67% ; 21 : 84%.

DCI-data : 17 : MH^+ : 406 (100) ; 18 to 21 : MH^+ : 420 (100).

D-Allo- and D-altro-2-(pentitol-1-yl)-pyridine 22 and D-allo- and D-altro-2-(pentitol-1-yl)-3(or 4,5,6)-methylpyridine 23, 24, 25 and 26.

A solution of 17 (or 18 to 21) (1.2 mmol) in 80% formic acid (20 ml) was heated at 100°C for 10 minutes. After cooling the solution was extracted with chloroform (2 x 30 ml) to remove all benzaldehyde formed. Then the solution was evaporated in vacuo to remove the formic acid.

20 ml of distilled water was added and the solution was made neutral by adding dilute ammonia.

Extraction with chloroform, followed by evaporation in vacuo of the water layer, left a white solid product, mainly ammonium formate. Most of the ammonium formate was removed by lyophilisation.

The allo-altro mixture was purified by reverse phase chromatography (RP8) using water/methanol (80/20). The solvent was removed under reduced pressure and the products were obtained as heavy syrups. Yield : 75-80%.

DCI-data : 22 : MH^+ : 230 (100) ; 23 to 26 : MH^+ : 244 (100).

Elemental analysis was considered unnecessary since all the products were chromatographically pure.No peaks from foreign

products could be detected in the M.S. and in the ^{13}C-NMR-spectra.

D-Allo- and D-altro-2-(1-O-methylsulphonyl-2,4:3,5-di-O-benzylidene-pentitol-1-yl)-pyridine 28 and the corresponding picoline derivatives 29 to 32.

To a stirred solution of 17 (or 18 to 21) (2 mmol) in dry pyridine (20 ml) methanesulphonyl chloride (690 g = 6 mmol ; d^{20}=1.474) was added dropwise at room temperature and the mixture was kept overnight. After addition of water, saturated with $NaHCO_3$, the solution was repeatedly extracted with chloroform. The combined chloroform layers were dried on $MgSO_4$ and evaporated leaving a brown syrup. Chromatography on silylated silicagel with ethyl acetate gave the methylsulfonyl derivative 28 (or 29 to 32) as pale yellow foams. Yield : 80%.

DCI-data : 28 : MH^+ : 484 (100) ; 29 to 32 : MH^+ : 498 (100).

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