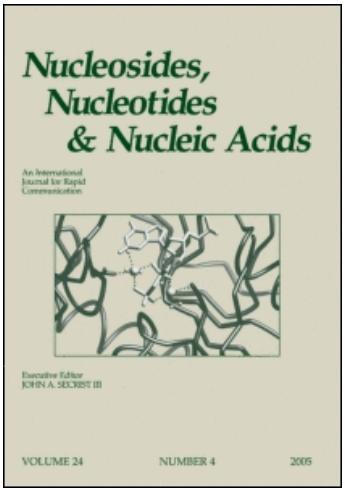

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Synthesis And Spectral Properties of Uric Acid Ribosides

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SYNTHESIS AND SPECTRAL PROPERTIES OF URIC ACID RIBOSIDES

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ABSTRACT. Ribosylation of trimethylsilyl uric acid by tetra-O-acetyl-ß-D-ribofuranose in the presence of trimethylsilyl trifluoromethanesulfonate as the condensing agent was studied at various ratio of the reactants. As a result uric acid N_7-monoriboside and N_7,N_3-diriboside were obtained and their spectral properties examined.

INTRODUCTION

During the past few decades two isomeric uric acid ß-D-ribofuranosides and their 5'-monophosphates, viz., N_3- and N_9-glycosides, were isolated from the natural sources (1-3). The determination of the structure of these compounds was the subject of a number of investigations (1,2, 4). The problem of ascertaining the structure of uric acid ribosides was complicated by the fact that different authors have isolated both isomers from the same sources by highly similar methods. The matter was discussed in some detail by Forrest et al. (1) and by Holmes and Robins (4).

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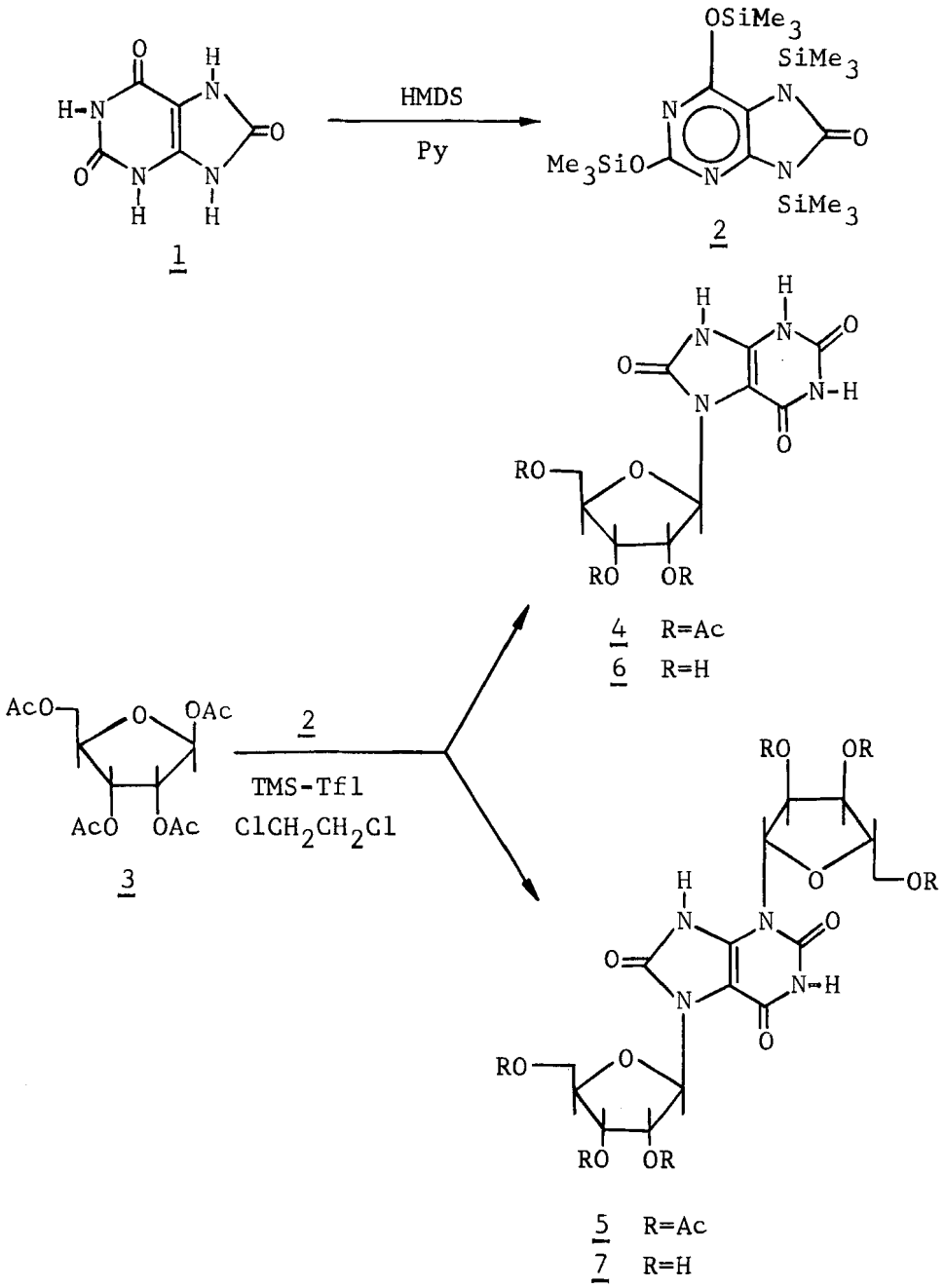
Synthesis of uric acid N_3-riboside was accomplished by purine ring closure after attachment of the ribofuranosyl fragment (5), and the N_9-isomer was synthesized starting from 8-bromoguanosine (4). Glycosylation of uric acid 1, as its tetratriethylsilyl derivative, by 1-bromo-2,3,5-tri-O-benzoyl-D-ribofuranose in the presence of $AgClO_4$ was studied by Birkofer et al., who suggested that the compound obtained was the N_3-riboside (6).

As far as the biological role of uric acid ribosides is concerned, there exist several different viewpoints (for a discussion of this matter see Smith and Lawing (7)). Recently two groups of investigators have proposed that uric acid and its ribosides may have a function of the antioxidant defense of organisms (7,8). This prompted us to investigate the biological properties of uric acid glycosides in more detail. The present study is an account of the synthesis of uric acid ribosides by means of glycosylation of uric acid tetra-trimethylsilyl derivative (TMS-UA, 2) by tetra-O-acetyl-ß-D-ribofuranose (3) in the presence of trimethylsilyl trifluoromethanesulfonate (TMS-triflate, TMS-Tfl) (9).

RESULTS AND DISCUSSION

Condensation of 1 equiv of TMS-UA 2 in 1,2-dichloroethane with 0.9 equiv of acetate 3 and 1.2 molar equiv of TMS-Tfl at 5°C for 72 h and subsequent work-up of the reaction mixture afforded a 81% yield of acetate 4. Treatment of 4 with methanolic ammonia furnished uric acid N_7-ß-D-ribofuranoside (6) in a yield of 58%. The ribosylation of 1 equiv of TMS-UA 2 with 3 equiv of acetate 3 and 1.2 molar equiv of TMS-Tfl at 5°C for 72 h followed by heating of the reaction mixture at 50°C for 5 h afforded a 52% yield of the diriboside 5 after column chromatography on silica gel. Monitoring of the reaction course by TLC showed that the primary product was monoriboside 4, which was then converted into diriboside 5. Besides ribosides 4 and 5, in the reac-



SCHEME 1

tion mixture other compounds were detected which were not isolated in pure state. Deacetylation of 5 with methanolic ammonia furnished uric acid N_7,N_3-di-(ß-D-ribofuranoside) (7) in a yield of 55%.

The purity of ribosides 6 and 7 was checked by high pressure liquid chromatography (HPLC) and by ^{1}H NMR spectroscopy with maximal amplification of resonance signals. It must be noted that in some experiments isolated compounds 6 and 7 contained some impurities (most probably isomeric ribosides) the total amount of which did not exceed 5%.

The structures of compounds 6 and 7 were suggested by careful examination of ^{1}H and ^{13}C NMR and UV spectral data and by comparison with the related nucleosides. TABLE 1 lists ^{1}H NMR data for uric acid monoriboside 6 and diriboside 7. To compare the spectral properties, uric acid N_9-riboside 8 (4) and 8-oxoadenosine 9 (10) were synthesized. TABLE 1 also includes ^{1}H NMR data for xanthosine (10). The ^{3}J(H,H) values of the ribose moieties of compounds 6 and 7 (cf. with those of N_9-riboside 8) confirm the ß-anomeric configuration with the predominant population in the C_2,-endo conformation (11,a). Monoriboside 6, as it follows from the ^{1}H NMR data, and in agreement with TLC and HPLC analysis, is not the uric acid N_9-derivative. Of interest is the determination of the ribosylation site of nucleoside 6 are δ H_1, and H_2, values as well as their comparison with those of compounds 8-10. A downfield shift of the anomeric proton H_1, is attributed to the close proximity of the anisotropic carbonyl group. It could take place in the case of the ribosyl fragment attachment to the N_7-, N_3- or N_1-atom of the base. For instance, 3-(ß-D-ribofuranosyl)xanthine showed the H_1, resonance at lower field (6.22 ppm) (12) than the H_1, of xanthosine. Attachment of the ribosyl moiety to the N_3- or N_1-atom of the base seems unlikely because a downfield shift could be expected in both cases not only for the anomeric proton but also for H_2,, and an upfield shift for H_4, as compared with the respective resonances of N_9-riboside (cf. the data by Schweizer et al. (11) and Moffatt

TABLE 1

^{1}H NMR spectroscopy data for compounds 6-10

Compounds	Chemical shifts, δ (ppm)							Coupling constants, J(Hz)					
	H-2, H-8	H-1'	H-2'	H-3'	H-4'	H-5' H-5"	Other protons	1',2'	2',3'	3',4'	4',5'	4',5"	5',5"
6*		6.09d	4.26dd	4.04dd	3.99m	3.69dd 3.64dd		8.0	5.6	1.9	1.9	2.8	12.1
7*		6.09d	4.24dd	4.04dd	3.99m	3.69dd 3.64dd		8.0	5.6	1.9	1.9	2.8	12.1
		5.82d	4.66dd	4.04dd	3.75m	3.57dd 3.40dd		7.1	7.1	3.7	3.5	5.3	11.9
8**		5.64d	4.26dd	4.0m		3.70m	10.96s(2H,NH) 11.08s(1H,NH)	7.5	6.5				
9**	8.02s	5.72d	4.88dd	4.14dd	3.90m	3.56m	6.58s(2H,NH_2) 10.40s(1H,NH)	6.0	5.0	3.0			
10**	7.84s	5.74d	4.26dd	4.0m		3.70m	10.88s(1H,NH)	6.5	5.0				

* A 360 MHz spectrum

** A 100 MHz spectrum

et al. (13,14) for the related pairs of N_9- and N_3-isomers as well). Unfortunately, the $H_{2'}$ shift of 3-(ß-D-ribofuranosyl)xanthine is not indicated (12). Based on the ^1H NMR data, the attachment of the ribosyl moiety of compound 6 to N_7-atom of the heterocycle seems more likely. It has been found earlier for isomeric pairs of guanine, hypoxantine and 3-deazaguanine glycosides that by going from N_9- to N_7-isomer the anomeric proton resonance is shifted downfield by 0.18-0.73 ppm (15-20). Recently we found that $\Delta\delta$ $H_{1'}$ value for guanine N_9- and N_7-xylofuranosides is 0.40 ppm (21; cf. also with data in Ref. 19,20). The $\Delta\delta$ $H_{1'}$ value for N_9-riboside 8 and newly synthesized compound 6 show fair agreement with these data. Moreover, the absence of an appreciable shift of the $H_{2'}$ resonance in going from guanine and hypoxanthine N_9- to N_7-glycosides ($\Delta\delta$ $H_{2'}$, $\leq$ 0.15 (19-21)) is also diagnostic for the ribosylation site of nucleoside 6.

Compound 7 has two ribosyl moieties, δ and $^3J(H,H)$ magnitudes one of which perfectly coincide with those for monoriboside 6. This fact is not surprising if we take into account the method for diriboside 7 synthesis. The second ribose fragment may be attached to the N_3- or N_1-atom of the base, if one bears in mind the downfield shift of the $H_{1'}$ and $H_{2'}$ resonances and the upfield shift of the $H_{4'}$ resonance in comparison with those for N_9-riboside 8 and xanthosine 10 (cf. data for 8-oxoadenosine as well). The ^1H NMR data for the diriboside 7 cannot give more definitive proof for the second ribosylation site.

In order to gain further insight into the structures of compounds 6 and 7, we have studied the ^{13}C NMR spectra of them along with N_9-riboside 8 and xanthosine (10) (TABLE 2). Assignments of the ^{13}C resonances of the carbohydrate fragments of the compounds studied are based on the literature data (22,23) (assignments of $C_{2'}$ and $C_{3'}$ as Mantsch and Smith have reported for uridine (24)) and the characteristic $^1J(C,H)$ values found by one of us earlier (25,26). The absence of C-H fragments in the heterocyclic moiety of uric acid ribosides 6, 7 and 8 caused difficulties in

TABLE 2

^{13}C NMR spectroscopy data for compounds 6-8 and 10

(the $^{1}J(C,H)$ values (Hz) are given in parenthesis)

Compounds	Aglycon						Carbohydrate moiety			
	C-6	C-2	C-4	C-8	C-5	C-1'	C-2'	C-3'	C-4'	C-5'
6	152.82*	149.31	135.77	152.35*	98.91	87.48 (166.2)	70.93 (142.8)		85.43 (147.0)	61.20 (140.9)
							70.57 (147.9)			
7	152.49*	148.88*	136.08	151.34*	98.57	87.55 (~168+)	70.94 (~148+;~152+)		85.49 (~148+)	61.03 (140.4)
						87.01 (162.3)	70.57 (147.7)		84.45 (147.6)	62.14 (139.1)
							70.09 (147.7)			
8	153.80	149.00	136.94	150.83	96.94	86.61 (166.2)	71.98 (148.4)		85.62 (148.4)	61.65 (143.2)
							71.49 (155.8)			
$\Delta\delta^{\times} = \delta^{8} - \delta^{6}$	+0.98	-0.31	+1.17	-1.52	-1.97	-0.87			+0.19	+0.45
10	157.84	150.57	139.68 (216.5)	135.47	116.23	88.73 (165.4)	73.94 (146.5)	70.77 (149.7)	86.07 (146.5)	61.20 (141.6)
$\Delta\delta^{\times} = \delta^{10} - \delta^{8}$	+4.04	+1.57	+2.74	-15.36	+19.29	+2.12	+2.20	-1.0	+0.45	-0.45

* Unequivocal assignments for the resonances corresponding to the indicated carbon atoms have not been obtained

\+ The value is not determined precisely owing to overlap of the resonances

× Positive values indicate shifts to a lower field, and negative ones to a higher field

assigning the ^{13}C resonances of the base, except for the upfield singlet of C_5 (22,23). For this reason we attempted to employ the ^{13}C NMR spectrum of xanthosine (22) as the basis for the assignments of the purine ^{13}C resonances for uric acid N_9-riboside 8 and then for compounds 6 and 7. The general pattern of chemical shift changes upon substitution of a hydroxyl group at the C_8 position of purine have been studied in considerable detail by Uesugi and Ikehara (27).

The C_6 resonance position in the ^{13}C NMR spectrum of xanthosine (22) is anomalously shifted downfield (δ_{TMS} 164.5 ppm) as compared with related compounds - inosine and guanosine (cf., e.g., with data cited (22), and (27), as well). This observation prompted us to measure the ^{13}C NMR spectrum of xanthosine under conditions where all the resonances of the heterocyclic base had a high intensity. Good agreement was found with earlier results (22) in regard to the resonances of the carbohydrate fragment but discrepancies were found for the resonances of the base. The reason for these differences remains obscure. The coupled spectrum of xanthosine allowed us to assign the resonance of C_8 at 135.47 ppm from its coupling with H_8 ($^1J(C_8,H_8) = 216.5$ Hz). Assignments of the C_6,C_2 and C_4 resonances stem from comparisons with those of guanosine (22,27) and with the δ ^{13}C variations observed in the heterocycle in going from adenosine to inosine (27).

As might be expected, the differences between the chemical shifts in going from xanthosine to uric acid N_9-riboside 8 are consistent with those for similar changes in adenosine, inosine and guanosine (27). On the contrary, when the site of ribosylation is changed from N_9 8 to N_7 6, one detects only the slight alterations of the resonances of the aglycon and carbohydrate fragments as distinct from those for N_9- and N_7-glycosides of adenine and hypoxanthine (23,26). This notwithstanding the compound 6 has in all likelihood the N_7-riboside structure. It should be noted here that changes in bond orders as well as in charge densities both affect the ^{13}C resonance positions of hetero-

cycles (28,29). As might be expected, both of these factors change slightly in going from the N_9- to the N_7-riboside of uric acid. The differences between the chemical shifts are caused, therefore only by the influence of the ribosyl fragment which of itself did not shift considerably the ^{13}C resonance positions of the aglycon (23,28). At the same time, the δ ^{13}C variations of C_6, C_4 and C_5 for the isomeric riboside pairs 8 and 6 give evidence of N_7-attachment of the carbohydrate fragment of the latter compound. When passing from the N_7-isomer to the N_9-riboside (i) the C_6 resonance is shifted downfield by +0.98 ppm due to the removal of the steric interaction between the ribose moiety and the 6-oxo function (23); (ii) the C_4 and C_5 resonances are shifted in an opposite direction by analogy with the data obtained for the isomeric purines (23,28).

Attachment of the second ribosyl fragment to the uric acid caused only a slight shift of the resonances of the aglycon in comparison with the monoriboside 6 due largely to the lack of alteration of the bonding patterns. Unfortunately, assignments of the C_6, C_2 and C_8 resonances of diriboside 7 are not definitive in consequence of which the ^{13}C NMR spectrum was unrevealing with respect to the site of the second ribosyl moiety attachment.

A comparison of the UV absorption data of the monoriboside 6 with those of the N_7-methyl uric acid (1,30) lends further support to the above structure assignment. A progressive bathochromic shift in the long-wavelength maxima and an increase of the molar extinction coefficients in the UV absorption spectra of the monoriboside 6 is observed upon changing the pH from 1 to 13 (TABLE 3), as well as the bond position furnished additional proof for the N_7-attachment of the ribosyl moiety. The UV spectra of diriboside 7 were found to be very similar to those reported for the uric acid 3,7-dimethyl derivative when compared with the reported UV absorption spectral data for the 1,7-, 3,7- and 9,7-dimethyl derivatives of uric acid (30). The following peculiarities are supportive of the N_7,N_3-isomeric struc-

TABLE 3

UV spectroscopy data for compound 6 and 7

Compound	pH	UV absorption			
		λ_{max}(nm)	$\varepsilon \cdot 10^{-3}$	λ_{min}(nm)	$\varepsilon \cdot 10^{-3}$
6	1	290	11.21	258	3.43
		~232 sh	5.90		
	7	295	12.14	258	3.17
		232	6.46	221	5.80
	13	299	14.24	257	2.11
		~218 sh	19.50		
7	1	290	10.74	256	2.76
		~232 sh	6.30		
	7	300	15.60	261.5	4.25
		~240 sh	4.24		
		~220 sh	13.16		
		202	17.19		
	13	297.5	12.49	259	1.30
		~210			

ture for diriboside 7: (i) the characteristic displacement of the long-wavelength maxima and the molar extinction coefficient changes in going from pH 1 to 13; (ii) the UV spectrum of the diriboside 7 at pH 13 displayed a broad minimum within 230-270 nm, whereas uric acid 1,7- and 3,7-dimethyl derivatives reveal weak absorption about 250 nm at the same conditions which is, however, considerable lower in the case of the 3,7-isomer.

In toto, the spectral data considered herein clearly points to the N_7-riboside structure for compound 6 and allows us to suggest the N_3,N_7-isomeric structure for diriboside 7 as the most likely one.

The biological activity of the synthesized compounds and the other uric acid glycosides will be reported elsewhere.

EXPERIMENTAL

UV spectra were recorded on a Specord UV-VIS (Carl Zeiss, GDR). ^{1}H NMR spectra were obtained on a INM PS-100 (JEOL, Japan) and WM-360 (Bruker-Physik AG, FRG) spectrometers. ^{13}C NMR spectra of 0.08 M Me_2SO-d_6 solutions were obtained on a Bruker WM-360 spectrometer operating at 90.56 MHz in the Fourier transform mode at a probe temperature of 35°C. Chemical shifts are measured from tetramethylsilane (TMS) employed in all cases as internal standard. IR spectra were recorded on a Perkin-Elmer 257 spectrometer (USA) in petrolatum oil.

Analytical HPLC was conducted on a Du Pont (model 850, USA) instrument using 280 nm UV detection and a 9.4 x 250 mm column of Zorbax ODS; solvent: acetonitrile (5%)-phosphoric acid (0.1%) - water (94.9%); flow rate 5 ml/min; retention time: N_7-riboside 6 - 4.4 min; N_9-riboside 8 - 5.0 min; diriboside 7 - 7.9 min.

Optical rotations were measured on a Perkin-Elmer model 241 digital spectropolarimeter using 1.0 dm cell. Melting points were determined using a Boethius (GDR) hot-stage microscope and are uncorrected. Thin-layer chromatography (TLC) was carried out on silica gel A: Silufol UV-254 (Czechoslovakia) and B: F1500 LS254 (Schleicher & Schüll, FRG) plates by using the following solvent systems (v/v): 1) chloroform - methanol, 9:1; 2) chloroform - methanol, 4:1; 3) 2-butanol - acetic acid - water, 5:3:2; 4) the first eluent - chloroform, the second - system 3. Detection of compounds on silica gel was by ultraviolet light and with 0.1% naphthoresorcin in water-ethanolic (1:1, v/v) phosphoric acid (5%) spray followed by heating at 110°C for 5-15 min.

9-(ß-D-Ribofuranosyl)uric acid (8) was synthesized as described in (4): $[\alpha]_D^{20}$ -39.4° (c 0.502, 0.1 N NaOH), lit.

(4): $[\alpha]_D^{20}$ -41.2° (c 1.02, 0.1 N NaOH); R_f 0.45 (B,4); UV spectra data of the synthesized N_9-riboside 8 are in complete accordance with the data reported in (4). 8-Oxoadenosine (9) was synthesized as described in (10); R_f 0.14 (B,2), adenosine had R_f 0.21 at the same conditions; ^{13}C NMR spectrum of compound 9 was identical with that reported in (27). Xanthosine was purchased from Chemapol (Czechoslovakia) and was used without further purification, R_f 0.48 (B,4), 0.02 (B,2). Trimethylsilyl triflate was purchased from Fluka AG (Switzerland).

Column chromatography was done on Silica gel L 100/250 (Czechoslovakia) using 280 nm UV detection. Analytical samples were dried in vacuo over P_2O_5 at 80°C for 6 h.

7-(2,3,5-Tri-O-acetyl-ß-D-ribofuranosyl)uric acid (4).

Uric acid (1) (1.68 g, 10.0 mmol) was refluxed in a mixture of hexamethyldisilazane (60 ml) and dry pyridine (10 ml) until dissolved completely. The reaction mixture was evaporated to dryness in vacuo, supplemented with toluene (20 ml) and re-evaporated. The residue was dissolved in 1,2-dichloroethane (50 ml), cooled to 5°C, and acetate 3 (2.86 g, 9.0 mmol) and trimethylsilyl triflate (2.67 g, 2.15 ml, 12.0 mmol) were added with stirring. The reaction mixture was kept at 5°C for 72 h and then poured with vigorous stirring into a $NaHCO_3$ (7.0 g) suspension in a mixture of chloroform (200 ml) and acetonitrile (300 ml) followed by stirring for 30 min. A precipitate was filtered off and washed with chloroform (3 x 50 ml). The pooled filtrates were evaporated to dryness in vacuo. The residue was dissolved in a minimal amount of ethanol and treated with ether (200 ml). The precipitate formed was filtered off and recrystallized from ethanol to give acetate 4 (3.10 g, 81%); m.p. 191-193°C; R_f 0.16 (A,1); $[\alpha]_D^{20}$ +35.7° (c 0.67, MeOH); UV (MeOH) λ_{max} 293 nm (ε 12110). IR (cm^{-1}): ν_{max} 1750 (C=O acetate); 1610 and 1560 (purine ring). Found: C 44.93; H 4.20; N 13.27%. $C_{16}H_{18}N_4O_{10}$. Calculated: C 45.08; H 4.25; N 13.14%.

7-(ß-D-Ribofuranosyl)uric acid (6)

Acetate (4) (3.10 g, 7.27 mmol) was dissolved in methanol saturated with ammonia at 0°C (50 ml), the reaction mixture was kept at 20°C for 24 h, and evaporated to dryness in vacuo. The residue was dissolved in 90% aqueous methanol, silica gel (15 cm^3) was added to the solution and the solvents were distilled off in an evaporator. Silica gel with the substance was put on the top of a silica gel (100 cm^3) column. Elution with chloroform (500 ml) and then with a linear gradient from chloroform (500 ml) to ethanol (500 ml) afforded the riboside 6 (1.26 g, 58%) as an amorphous powder; m.p. >200°C (decomp.); R_f 0.59 (B,4); $[\alpha]_D^{20}$ -34.2° (c 0.50, 0.1 N NaOH). Found: C 37.33; H 4.38; N 17.24%. $C_{10}H_{14}N_4O_8$. Calculated: C 37.74; H 4.43; N 17.61%.

3,7-Di-(2,3,5-tri-O-acetyl-ß-D-ribofuranosyl)uric acid (5)

To a solution of the trimethylsilyl derivative of uric acid, obtained from 1 (1.68 g, 10.0 mmol) as described above, in 1,2-dichloroethane (50 ml) at 5°C were added under stirring acetate 3 (9.54 g, 30.0 mmol) and trimethylsilyl triflate (2.67 g, 2.15 ml, 12.0 mmol). The reaction mixture was kept at 5°C for 72 h and then heated at 50°C for 5 h, and processed as described above. The crude reaction product was purified by column chromatography on silica gel (100 cm^3) with chloroform (500 ml) and then with 99:1 chloroform - ethanol (500 ml) to give acetate 5 (3.58 g, 52%) as a foam; R_f 0.47 (A,1); $[\alpha]_D^{20}$ +26.2° (c 0.573, MeOH). UV (MeOH): λ_{max} 289 (ε 10360). IR (cm^{-1}): ν_{max} 1750 (C=O acetate); 1650 and 1550 (purine ring). Found: C 47.53; H 4.63; N 8.22%. $C_{27}H_{32}N_4O_{17}$. Calculated: C 47.37; H 4.71; N 8.18%.

3,7-Di-(ß-D-ribofuranosyl)uric acid (7)

Acetate (5) (2.65 g, 4.81 mmol) was dissolved in methanol saturated with ammonia at 0°C (50 ml), the reaction mixture was kept at 20°C for 24 h, and evaporated to dryness in vacuo. The crude reaction product was purified by

column chromatography on Dowex AG 50 x 8 (H^+-form, 70 cm^3) in water to give diriboside 7 (1.14 g; 55%); m.p. 188-190°C (from ethanol); R_f 0.35 (B,4); $[\alpha]_D^{20}$ -31.3° (c 0.635, 0.1 N NaOH). Found: C 41.17; H 5.14; N 12.69%. $C_{15}H_{20}N_4O_{11}\cdot 0.5\,H_2O$. Calculated: C 40.82; H 4.80; N 12.70%.

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