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Nucleosides, 38[1]

The Ribonucleosides of Allopurinol[2]

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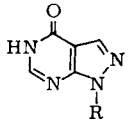
Of the various conceivable ribonucleosides of allopurinol, the *N*-1-, *N*-2-, and *N*-5-isomers (**9c** – **11c**) as well as the 1,5- and 2,5-bis-ribosylated derivatives **6c** and **7c** have been prepared via stannic chloride-induced glycosylation of bis(trimethylsilyl)allopurinol **4** with acylated ribofuranoses (**5**). Trimethylsilyl triflate as catalyst in addition produced the O^4-ribosylated isomer **8a**. – The structures of the products were secured from UV, ^{1}H, and ^{13}C NMR data. – Their xanthine oxidase inhibitory activity was evaluated.

Nucleoside, 38[1]

Die Ribonucleoside des Allopurinols[2]

Von den verschiedenen Ribonucleosiden des Allopurinols wurden die *N*-1-, *N*-2- und *N*-5-Isomeren (**9c** – **11c**) sowie die 1,5- und 2,5-bis-ribosylierten Derivate **6c** und **7c** durch $SnCl_4$-induzierte Glycosylierung von Bis(trimethylsilyl)allopurinol **4** mit acylierten Ribofuranosen (**5**) dargestellt. Trimethylsilyl-triflat als Katalysator bildete zusätzlich das O^4-ribosylierte Isomere **8a**. Die Konstitutionen der Produkte wurden aus UV-, ^{1}H-NMR- und ^{13}C-NMR-Daten abgeleitet. Die Fähigkeit der Produkte, Xanthin-Oxidase zu inhibieren, wurde untersucht.

Allopurinol, 1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (**1**), synthesized by *Robins* and by *Schmidt* and *Druey* 25 years ago[3], has after discovery of its xanthine oxidase inhibitory properties[4] developed into a major therapeutic tool for controlling gout and related metabolic disorders[5]. The chief metabolite in mammalian systems is oxipurinol, the 6-oxo derivative of **1**, which similarly is an inhibitor of xanthine oxidase. This primary effect is augmented by secondary effects on pyrimidine and purine biosynthesis caused by minor metabolites such as allopurinol 1-ribonucleotide (**2**), which like 6-azauridine-5′-phosphate[6] inhibits orotidylate decarboxylase[7] and, thus, has high potential as an antiviral and antitumor agent. The 1-riboside **3**, on the other hand, formed via direct ribosylation of **1** or via dephosphorylation of **2**, is entirely nontoxic in mammals[8], yet has impressive antiparasitic properties[9].



1: R = H

2: R =

3: R =

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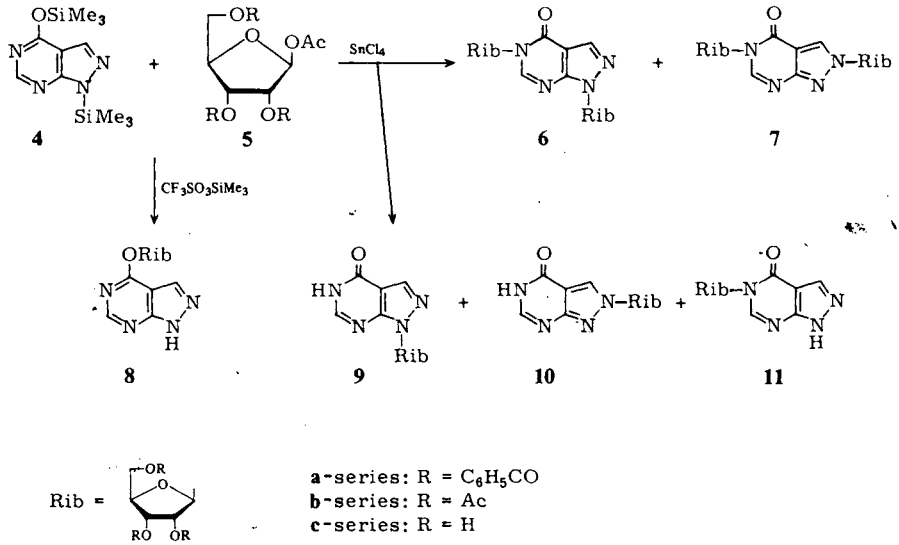
These remarkable pharmalogical attributes of allopurinol and its metabolic products lured us into the synthesis of analogs specifically modified in the heterocycle as well as in the attachment of the ribose portion in nucleosides thereof[2]. In this paper we report the results on the synthesis of the various isomeric ribosides and bis-ribosyl derivatives of allopurinol, those on the benzologous extension of the allopurinol skeleton being subject of ensuing communications[10].

Ribosylations of Allopurinol

The stannic chloride-catalysed *N*-glycosylation of silylated pyrimidines with fully acylated sugars[11] has been shown to be also capable of preparing purine nucleosides from silylated purines[12]. Application of this procedure to a silylated allopurinol, e. g. **4**, appeared to be propitious to the synthesis of **3** *and* its isomers, since in analogy to the respective glycosylations of bis(trimethylsilyl)hypoxanthine[13] ribosylation would be expected to occur in the pyrazol as well as in the pyrimidine portions of **4**.



The bis(trimethylsilyl)allopurinol required was readily obtained in crystalline form by refluxing **1** in hexamethyldisilazane, and was characterized as the 1,O^4-disubstituted derivative **4** on the basis of spectral, primarily ^{13}C NMR data (cf. below). When **4** was reacted with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**5a**) in the presence of stannic chloride in dichloroethane at 60°C, invariably, mixtures of five compounds resulted, comprising bis- and monoribosylated products in an approximate ratio of 3:2 (TLC). Separation was readily achieved on silica gel by preparative layer chromatography or HPLC techniques, affording the 1,5- and 2,5-bis-ribosides **6a** and **7a** in yields of 38 and 9% (HPLC), respectively, whilst the three monoribosides were obtained in 17% (*N*-1-riboside **9a**), 7% (*N*-2-isomer **10a**), and 12% yield (*N*-5-riboside **11a**). From these preparative data – the 1-, 5-, and 1,5-ribosylated compounds com-

prise about 80% of the total products isolated, allowing to infer a similar composition for the reaction mixture – the regioselectivity of the glycosylation reaction may be assessed in such, that ribosylation occurs with nearly equal ease at the *N*-1 and *N*-5 positions of the heterocycle under these conditions, whereas the nucleophilicity of *N*-2 is considerably lower. The preference of *N*-1 over *N*-2-ribosylation is, in fact, paralleled by glycosylations of 4-benzamidopyrazolo[3,4-*d*]pyrimidine via the chloromercuric or the fusion procedures[14].

When replacing stannic chloride in this ribosylation by trimethylsilyl trifluoromethanesulfonate (TMS triflate) – a catalyst propagated as being more regioselective with silylated pyrimidines as well as with N^6-benzoyl-1,N^6-bis(trimethylsilyl)adenine[15] – the riboside mixture resulting from a reaction at room temperature contained no bis-ribosylated products yet aside the *N*-1- (**9a**) and *N*-5-nucleosides (**11a**), a further, more polar allopurinol riboside as the major product. It was isolated in 22% yield and identified on the basis of spectral data (cf. below) as the O^4-substituted compound **8a**. When conducted at higher temperature (2 h, 80°C), however, the TMS triflate-induced ribosylation of **4** gave rise to a mixture of mono- and bis-ribosides similar to that obtained with $SnCl_4$, with no O^4-glycosylated product (**8a**) being detectable. This appears to indicate that under the more forcing conditions complete $O^4 \rightarrow N\text{-}1/N\text{-}5$-transribosylation had occured.

Another ribosylation procedure recently promoted as being essentially regiospecific[16] comprises the $SnCl_4$-catalyzed glycosylation with **5b** in the absence of silyl protecting groups in the heterocycle. Applying this procedure which gave useful results with adenine, 6-chloro-, and 6-mercaptopurines[16], to allopurinol (**1**) with either **5a** or **5b** as the sugar component failed to yield products under a variety of conditions.

When using peracetyl-β-D-ribofuranose **5b** for the ribosylation of **4**, mixtures of practically identical product distribution are obtained with $SnCl_4$/dichloroethane (4 h, 60°C) or with BF_3-etherate/dioxane (30 min, reflux), containing the three mono-ribosides (**9b – 11b**), the *N*-1, *N*-5- and the *N*-2, *N*-5-bis-ribosides in an approximate (TLC) 2:2:1 ratio. Whilst the latter two, i. e. **6b** and **7b**, were readily separated by preparative layer chromatography on silica gel and were characterized as analytically pure amorphous products, the separation of the former proved difficult.

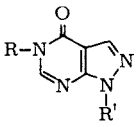
De-*O*-benzoylation of the blocked nucleosides **6a**, **7a** and **9a – 11a** with sodium methoxide/methanol afforded the respective free allopurinol ribosides **9c – 11c** and the bis-ribosyl derivatives **6c** and **7c**, which were readily characterized by analytical and spectral data (cf. below). Similar deblocking of the O^4-riboside **8a**, however, produced a product, presumably **8c**, which was difficult to characterize due to its tendency to hydrolyze to **1** and ribose. This instability of the O^4-glycosidic lactim ether type linkage is not unexpected[17] and is similarly observed in acid medium, brief heating (80°C) in 2 N acetic acid being sufficient to convert **8a** quantitatively into allopurinol; either of the *N*-ribosides was entirely unaffected by these conditions.

De-*O*-acetylation of the peracetates **6b** and **7b** was effected with methanolic sodium methoxide or methanolic ammonia in the usual fashion. A somewhat peculiar result provided the deblocking of the crude mono- and bis-riboside mixture (**6a, 7a, 9a – 11a**) with methanolic ammonia, since from the reaction mixture a product separated in

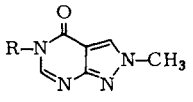
yields of up to 12%, which proved (vide infra) to be the 5-ribosyl-allopurinol (**11c**), crystallizing with one mol of acetamide in well-shaped needles of m. p. 205 – 206 °C. Thus, it appears likely, that the previously described product[18] of m. p. 201 – 202 °C and λ_{max} = 251 nm (pH 2) – rotation and yield were not disclosed – for which structure **9c** was claimed[19], in fact represented the respective *N*-5-isomer **11c**, since it was prepared *via* BF_3-catalyzed ribosylation of sirupy **4** with **5b**.

Structural and Configurational Characterization of Products

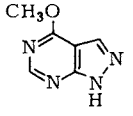
Site of ribosylation and β-configuration of the allopurinol ribosides prepared was established by correlation with literature data where feasible (**9c** and **10c**), and, more convincingly, on the basis of UV, ^1H, and ^{13}C NMR data (Fig. 1, Tables 1 and 2), which became particularly persuasive when set against the spectra of the corresponding methylated allopurinols **12** – **16**.



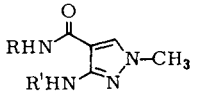
12: R = H; R' = CH_3
13: R = CH_3; R' = H
14: R = R' = CH_3



15: R = H
16: R = CH_3



17



18: R = H; R' = CH_3
19: R = CH_3; R' = H

Preparative routes to the various mono- and dimethylated allopurinols as well as their characterization are well established[21 – 24]. However, when we prepared 1,5-dimethylallopurinol (**14**) and its 2,5-dimethyl analog **16** by methylation of **1** with dimethyl sulfate/2 N NaOH[22], not only **14** and **16** were obtained but a mixture of at least four additional components, from which 1-methyl-3-(methylamino)-4-pyrazolecarboxamide (**18**) and the isomeric *N*-methyl-carboxamide **19** could be separated and characterized. Both pyrazole derivatives conceivably result from the alkaline hydrolysis of the pyrimidine ring in dimethyl-allopurinols, **19** originating from **16** as shown by experimental verification of this conversion, while **18** likely arises from an intermediate 2,7-dimethyl derivative of **1**.

Although the *N*-1-β-riboside of allopurinol has been obtained repeatedly, i. e. from mammalian[8a] or bacterial systems[25 – 27] and synthetically[2,28,29], the melting points given vary within an unusually wide range (164 – 271 °C). The value found by us for **9c** (172 – 174 °C) correlated well with those reported for a hydrazino-ribose-derived **9c** (171 – 173 °C)[28] and proved to be identical therewith[31] in terms of mixed melting point, UV (Fig. 1) and IR spectra. Corroborative evidence is provided by ^1H NMR data, the 4.5 Hz doublet for the anomeric proton (Table 1) proving the β-configuration, as well as by the ^{13}C-resonances (Table 2) the signal positions for the heterocyclic carbons showing very close resemblance to those for 1-methylallopurinol (**12**).

The structural assignment of allopurinol-2-riboside **10c** was based on its identity with an authentic sample[33], on the bathochromic shift of UV maxima at pH 7 and 11 as compared with the *N*-1-isomer **9c** (cf. Fig. 1) reflecting the ortho-quinoide distribution of electrons, and on NMR spectral data (Tables 1 and 2), here, too, ^{13}C-resonances being more cogent. The most profound change, as contrasted with the *N*-1-analog **9c**,

Table 1. Relevant Physical Data of Allopurinol Ribosides **6** – **11**

Site of Ribosylation	Compd.	$[\alpha]_D$ (*c*, solvent[a], °C)	UV-data in nm (lg ε) pH 7 λ_{max}	pH 7 λ_{min}	pH 11 λ_{max}	pH 11 λ_{min}	^{1}H-NMR (δ in ppm, *J* in Hz) 3-H[b]	6-H[b]	1′-H	1′′-H	solvent
N-1	**9a**	−62.6 (0.7, A, 20)	–	–	–	–	8.11	8.21	6.65 (d, 0.8)	–	[D$_6$]DMSO
	9c	−70.2 (0.5, M, 25)	252 (3.97)	233 (3.75)	271 (4.08) 254 (sh)	233 (3.59)	8.18	8.23	6.13 (d, 4.5)	–	[D$_6$]DMSO
N-2	**10a**	−66.3 (0.8, A, 20)	–	–	–	–	8.26	8.79	6.60 (d, 0.8)	–	[D$_6$]DMSO
	10c	−79.4 (0.6, M, 25)	261 (3.87)	233 (3.57)	284 (3.89)	240 (3.48)	8.08	8.63	5.90 (d, 2.5)	–	[D$_6$]DMSO
O^4	**8a**	−79.6 (1.0, A, 23)	–	–	–	–	8.63	8.64	≈6.5[c]	–	[D$_6$]DMSO
N-5	**11a**	−54.2 (0.9, A, 20)	–	–	–	–	>8.3[d]	8.48	6.40 (d, 0.8)	–	[D$_6$]DMSO
	11c	+18.4 (0.4, M, 25)	255 (3.86)	236 (3.68)	254 (3.82)	250 (3.81)	8.23	8.43	6.17 (d, 3.8)	–	[D$_6$]DMSO
N-1/N-5	**6a**	−72.3 (1.0, A, 20)	–	–	–	–	8.07	8.19	6.68 (s)	≈6.3[c]	$CDCl_3$
	6b	−5.4 (1.0, M, 20)	262 (3.90)	236 (3.60)	–	–	7.94	8.04	6.29 (d, 3)	≈6.3[c]	$CDCl_3$
	6c	−50.9 (0.8, M, 25)	254 (3.85)	236 (3.72)	no change		8.22	8.68	6.26[e]		[D$_6$]DMSO
N-2/N-5	**7a**	−91.1 (1.0, A, 20)	–	–	–	–	8.15	8.34	6.37 (d, 4)	≈6.3[c]	$CDCl_3$
	7b	−30.5 (1.0, M, 25)	261 (3.87)	237 (3.72)	–	–	7.98	8.14	5.86 (d, 2.8)	6.07 (m)	$CDCl_3$
	7c	−51.0 (1.0, M, 25)	261 (3.89)	241 (3.73)	256 (3.90)	245 (3.84)	8.56	8.88	5.86 (d, 3.5)	6.17 (m)	[D$_6$]DMSO

[a] Solvents: A = acetone; M = methanol. – [b] Assignments of 3-H and 6-H are tentative and may have to be interchanged. – [c] Complex multiplet, unresolved from other ribose protons. – [d] Unresolved from aromatic protons. – [e] Broad 2H-m.

Table 2. ^{13}C-NMR Data of Allopurinol Derivatives in δ (ppm); TMS as Internal Standard

Site of Substitution	Compd.	Solvent	C-3	C-3a	C-4	C-6	C-7a	C-1′	C-2′	C-3′	C-4′	C-5′
–	**1***)	[D$_6$]DMSO	134.14	105.63	157.91	147.57	154.45					
N-1	**9c**	[D$_6$]DMSO	135.62	106.36	157.39	148.62	153.02	88.60	73.65	70.98	85.39	62.40
	12*)	[D$_6$]DMSO	133.5	106.2	156.7	147.7	152.2					
N-2	**10c**	[D$_6$]DMSO	133.20	106.99	158.72	147.27	158.47	94.25	75.06	69.81	85.27	61.08
	15*)	[D$_6$]DMSO	129.2	107.9	159.5	146.2	158.2					
N-5	**11c**	[D$_6$]DMSO	133.78	104.47	156.99	147.17	153.80	87.25	74.85	69.68	84.91	60.58
	13	[D$_6$]DMSO	132.8	104.7	157.3	150.4	154.1					
O^4	**8a**	$CDCl_3$	129.47	106.38	168.31	150.55	153.50	93.61	73.11	71.08	80.21	63.42
	17*)	[D$_6$]DMSO	130.4	101.5	163.4	154.3	156.6					
N-1/O^4	**4**	$CDCl_3$	135.60	105.85	162.98	154.80	162.78					
N-1/N-5	**6c**	[D$_6$]DMSO	135.82	105.11	156.15	148.12	151.95	88.41	73.47	70.81	85.38	62.24
								87.77	74.96	69.19	84.74	60.14
	6b	$CDCl_3$	136.87	106.09	156.29	147.49	152.28	87.92	74.00	71.22	80.07	63.40
								86.72	73.79	70.14	79.98	62.92
	14	$CDCl_3$	134.68	105.65	157.58	149.11	151.77					
		[D$_6$]DMSO	133.74	105.03	156.60	151.08	151.79					
N-2/N-5	**7c**	[D$_6$]DMSO	128.90	105.73	157.65	146.88	157.55	94.57	75.05	69.79	85.23	60.95
								86.67	74.53	69.71	84.89	60.66
	16	[D$_6$]DMSO	128.41	106.34	158.01	149.01	158.11					

*) Data for **1** stem from ref.[32], those for **12**, **15** and **17** from ref.[23b].

is observed for the chemical shifts of C-7a and C-1', both showing a diamagnetic shift of 5 – 6 ppm which is obviously due to release of the deshielding effect of a 1-ribosyl moiety on C-7a and, in turn, of N-1 on the anomeric carbon.

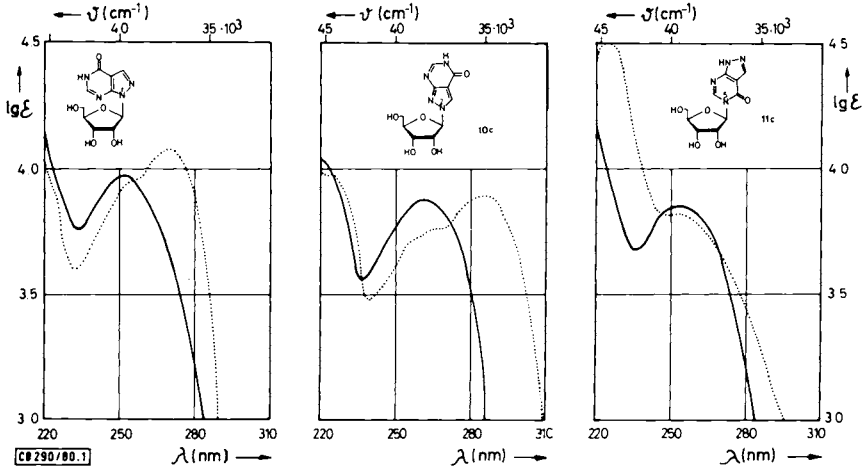


Fig. 1. UV spectra at pH 7 (neutral species, solid lines) and pH 11 (anion, dotted lines) of 1-(β-D-ribofuranosyl)allopurinol (**9c**), its *N*-2- (**10c**) and *N*-5-isomers (**11c**)

For the *N*-5-riboside **11c** site of ribosylation and β-configuration is already indicated by its positive rotation as compared with the strongly negative values for **9c** and **10c** (cf. Table 1), which was to be expected since **11c** structurally is distinctly analogous to a pyrimidine nucleoside ($[\alpha]_D$ for cytidine = +29.6° in water[34]) rather than to one derived from purines. A similar change is observed in going from inosine ($[\alpha]_D^{20}$ = −51° in water[35]) to its *N*-1-isomer (+43.6° in water[36]). As conclusive are the UV spectral data, the neutral species of the *N*-1- (**9c**) and *N*-5-ribosides (**11c**) affording curves (Fig. 1, pH 7) practically identical with that of allopurinol. Dissociation of the 5-NH in the pyrimidine moiety of **9c** and **10c** (pH 11, Fig. 1) expectedly[24] leads to a marked bathochromic shift, whilst ionization of the NH-proton in the pyrazole portion, as in **11c**, causes only minor changes. The ^1H[37] and ^{13}C NMR data are also consistent with the structure allotted.

The UV spectra of the bis-ribosylated allopurinols **6c** and **7c** closely resemble those of 1,5-dimethylallopurinol (**14**)[21] and its 2,5-dimethyl analog **16**[22], and, due to the absence of dissociable protons, are unaltered between pH 1 and 11. The ^{13}C NMR spectra of **6c** and **7c** correspond convincingly to what was to be expected from a superposition of a second set of ribose-resonances onto the *N*-1- and *N*-5-monoribosylated allopurinols, i. e. nearly identical values for the two ribose portions in the *N*-1,*N*-5-isomer **6c** as contrasted to clearly different chemical shifts for the anomeric carbons in the *N*-2,*N*-5-analog **7c** (cf. Table 2).

In **8a** the site of glycosylation unambiguously followed from the ready hydrolysis of the *O*-glycosidic linkage with mild acid, as expected[17] for imidoyl glycosides. Corroborative evidence was derived from ^{13}C NMR data, one marked feature being a downfield

shift by 6 – 7 ppm of the C-4 and C-6 resonances as compared with allopurinol or its 1- and 5-ribosides (cf. Table 2), whilst C-3 exhibited an adverse shift by 4 – 5 ppm. Very similar shift differences are observed for the respective *N*- and *O*-methyl derivatives **12**, **13**, and **17**[23b], and, in an analogous fashion, are found in the bis(trimethylsilyl)allopurinol **4** in which – as compared with the *N*-1,*N*-5-substituted dimethyl- and bis(ribosyl)allopurinols (**14** and **6b**, respectively, $CDCl_3$ data) – not only the C-4 and C-6 resonances are shifted paramagnetically but also that for C-7a, reflecting the deshielding by the trimethylsilyl group. This clearly proves a *N*-1/*O*[4]-substitution pattern for **4** rather than the alternate *N*-1/*N*-5-form.

Biological Evaluation

The properties of these ribonucleosides as inhibitors and/or substrates for xanthine oxidase were examined using conventional assay methods[38]. The *N*-1-riboside **9c**, being an excretion product of patients using allopurinol (**1**) for relief from gout[8a], had no xanthine oxidase inhibitory activity as expected[8b,27] and thus may be considered a detoxication metabolite of **1**. Similarly, the 1,5- and 2,5-bis-ribosides of **1**, i. e. **6c** and **7c**, had no effect, whilst the *N*-2- (**10c**) and *N*-5-isomers (**11c**) exhibited minor capacity to function as a substrate for, but not as an inhibitor of xanthine oxidase. The potential[9] antiparasitic activity of these allopurinol ribosides are being evaluated.

We express our appreciation to the *Fonds der Chemischen Industrie* for persistent support and to Dr. *R. A. Earl,* University of Michigan, Ann Arbor, for prolific discussions.

Experimental Part

Melting points: Bock-Monoskop, uncorrected. – IR: Perkin-Elmer 125. – Rotations: Perkin-Elmer 141. – NMR: Varian A-60 A and XL 100. – MS: Varian MAT 311 A. – TLC: Kieselgel F_{254} plastic sheets (Merck, Darmstadt), used to monitor the reactions and to ascertain the purity of the reaction products. Developers employed: A benzene/ethyl acetate (10:1 and 1:1), B dichloromethane/methanol (20:1), C ethyl acetate/water/n-propanol (4:2:1, upper phase), D chloroform/methanol (10:1), E n-butanol/water (95:5). The spots were visualized by UV light or by spraying with 80% aqueous sulfuric acid and charring at 110°C for 5 min. – Preparative chromatography: Kieselgel 60 (70 – 230 mesh, Merck).

1-(Trimethylsilyl)-4-(trimethylsilyloxy)-1H-pyrazolo[3,4-d]pyrimidine (**4**): A mixture of allopurinol (**1**, 2.1 g, 15.5 mmol), hexamethyldisilazane (7.0 g, 43 mmol), and a trace of ammonium sulfate (ca. 5 mg) was refluxed under exclusion of moisture until a clear solution was obtained (4 – 7 h). On cooling to room temperature partial crystallization occurred. Removal by filtration gave a first crop, evaporation of the filtrate in vacuo gave a second: 4.2 g (98%) colorless crystals of m. p. 86°C. – UV (dioxane): λ_{max} (lg ε) = 214 (4.21), 249 (3.87), 265 sh (3.77), λ_{min} = 229 nm (3.54). – ^{1}H-NMR ($CDCl_3$): δ = 0.38 and 0.56 (two s, each 9H, 2 $SiMe_3$), 8.15 and 8.45 (two s, each 1H, 3- and 6-H). – ^{13}C-NMR ($CDCl_3$): Table 2. – MS (70 eV): *m/e* = 280 (35%, M^+), 265 (100, M – CH_3).

$C_{11}H_{20}N_4OSi_2$ (280.5) Calcd. C 47.10 H 7.19 N 19.98 Found C 47.19 H 7.16 N 20.05

4 is quantitatively hydrolyzed to allopurinol on refluxing in aqueous ethanol.

Acylated allopurinol ribosides

$SnCl_4$-catalyzed ribosylation of **4** *with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose* (**5a**): To a solution of **4** (3.1 g, 11 mmol) and **5a** (5.0 g, 10 mmol) in 1,2-dichloroethane (100 ml) was added molecular sieve[39] (5 g) and $SnCl_4$ (1.2 ml, 10 mmol) and the mixture was stirred at 60°C for 6 h under careful exclusion of moisture. The molecular sieve was removed and the solution after dilution with 1,2-dichloroethane (300 ml) was extracted twice with aqueous $NaHCO_3$ solution and with water. Drying (Na_2SO_4) and evaporation to dryness left a colorless foam (3.2 g) which consisted (TLC in A, 10:1) of an approximate 2:1:2 mixture of 1,5-bis-riboside **6a** (R_F = 0.48), 2,5-bis-riboside **7a** (0.22), and the monoribosides **9a**, **10a**, and **11a** (R_F = 0.1). Separation by HPLC on silica gel (Waters Prep-LC system 500, prep pack silicagel cartridge) with toluene/ethyl acetate (10:1) afforded fractions of chromatographically (TLC in A, 1:1) uniform **6a** and **7a** and a mixture of **9a**, **10a** and **11a**, which was rechromatographed with toluene/ethyl acetate (1:1) to yield fractions of the pure compounds. Evaporation of the appropriate eluates usually gave syrups that crystallized on trituration with chloroform or acetone:

1,5-Dihydro-1,5-bis(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one (**6a**): 1.97 g (38%) from chloroform; m. p. 185–186°C; $[\alpha]_D^{20}$ = −72.3° (*c* = 1, acetone). – MS (FD): *m/e* = 1025 (100%, M^+ + 1), 1024 (80%, M^+). – ^{1}H-NMR ($CDCl_3$): Table 1.

$C_{57}H_{44}N_4O_{15}$ (1024.9)	Calcd.	C 66.79	H 4.33	N 5.47
6a:	Found	C 66.89	H 4.28	N 5.51
7a:	Found	C 66.74	H 4.24	N 5.43

2,5-Dihydro-2,5-bis(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one (**7a**): 0.45 g (9%) of colorless crystals ($CHCl_3$); m. p. 208–209°C; $[\alpha]_D^{20}$ = −91.1° (*c* = 1, acetone). – MS (FD): *m/e* = 1025 (90%, M^+ + 1), 1024 (100, M^+). – ^{1}H-NMR ($CDCl_3$): Table 1.

1,5-Dihydro-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one (**9a**): 0.95 g (17%) of colorless crystals from chloroform; m. p. 180–181°C; $[\alpha]_D^{20}$ = −62.6° (*c* = 0.65, acetone). – MS (FD): *m/e* = 581 (100%, M^+ + 1). – ^{1}H-NMR: Table 1.

$C_{31}H_{24}N_4O_8$ (580.5)	Calcd.	C 64.13	H 4.17	N 9.65
9a:	Found	C 63.91	H 4.14	N 9.54
10a:	Found	C 63.96	H 4.20	N 9.61
11a:	Found	C 64.06	H 4.09	N 9.58

2,5-Dihydro-2-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one (**10a**): 0.43 g (7%) of colorless crystals from chloroform; m. p. 210–212°C, after sintering around 140°C; $[\alpha]_D^{20}$ = −66.3° (*c* = 0.78, acetone). – MS (FD): *m/e* = 581 (100%, M^+ + 1). – Relevant ^{1}H-NMR data cf. Table 1.

1,5-Dihydro-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one (**11a**): 0.68 g (12%) of crystals from acetone; m. p. 236–237°C; $[\alpha]_D^{20}$ = −54.2° (*c* = 0.9, acetone). – MS (FD): *m/e* = 581 (M^+ + 1). – ^{1}H-NMR data see Table **1**.

Alternately, the allopurinol riboside mixture formed can be separated by PLC (1.5 mm layers of silica gel PF_{254} (Merck) on 20 × 40 cm glass plates) with benzene/ethyl acetate (10:1) to yield three zones, containing pure **6a** (16%, R_F = 0.48 in A, 10:1) and **7a** (6%, R_F = 0.22) together with an approximate 3:1:3 mixture of **9a** (R_F = 0.37 in A, 1:1), **10a** (0.23), and **11a** (0.49). The latter was rechromatographed on 10 plates to yield the pure monoribosides in yields of 9 (**9a**), 4 (**10a**), and 4% (**11a**).

Trimethylsilyl trifluoromethanesulfonate-induced ribosylation of **4** *with* **5a**

4-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyloxy)-1H-pyrazolo[3,4-d]pyrimidine (**8a**): A mixture of **4** (2.8 g, 10 mmol), **5a** (5.0 g, 10 mmol), trimethylsilyl triflate (1.8 ml, 10 mmol), and 1,2-

dichloroethane (100 ml) was stirred at ambient temperature for 6 h, followed by dilution with dichloromethane (700 ml) and extraction with saturated aqueous $NaHCO_3$ solution (2 × 100 ml). The organic phase was dried (Na_2SO_4), taken to dryness, and triturated with acetone (10 ml) and ether (ca. 50 ml) to yield 1.26 g (22%) of chromatographically uniform **8a** as colorless crystals of m. p. 207 – 210°C; $[\alpha]_D^{20} = -79.6°$ (c = 1.0, acetone). – MS (FD): m/e = 580 (100%, M^+). – ^{1}H- and ^{13}C-NMR: Tables 1 and 2.

$C_{31}H_{24}N_4O_8$ (580.5) Calcd. C 64.13 H 4.17 N 9.65 Found C 64.16 H 4.11 N 9.61

The mother liquor contained sizable amounts of the *N*-1- (**9a**) and *N*-5-isomers (**11a**), yet only traces of bis-ribosides.

Heating a solution of **8a** in 2 N acetic acid/methanol (1 : 2) at 80°C showed complete hydrolysis to allopurinol (TLC in B) after 45 min. All *N*-ribosides were stable towards these conditions.

$SnCl_4$-catalyzed ribosylation of **4** *with 1,2,3,5-Tetra-O-acetyl-β-D-ribofuranose* (**5b**): To a mixture of **4** (2.8 g, 10 mmol), **5b** (3.0 g, 9.4 mmol), and molecular sieve[39] (4 g) in 1,2-dichloroethane was added a solution of $SnCl_4$ (0.8 ml, 7 mmol) in the same solvent (20 ml), followed by stirring at 60°C for 4.5 h. Dilution with dichloroethane (400 ml), washing with saturated aqueous $NaHCO_3$ (50 ml), drying (Na_2SO_4), and evaporation to dryness left a syrup (3.6 g), which consisted of an approximate 2 : 1 : 2 mixture of the 1,5-bis-riboside **6b** (R_F = 0.68 in B), its 2,5-isomer **7b** (0.54), and the mono-ribosides **9b**, **10b**, and **11b** (R_F = 0.23, 0.17, and 0.26, resp.). Separation by PLC (20 plates, 3 developments) with dichloromethane/methanol (20 : 1) gave 3 well differentiated zones that were excised and eluted with acetone.

Evaporation of the fast moving zone gave 710 mg (23%) of *1,5-dihydro-1,5-bis(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one* (**6b**) as a chromatographically uniform foam; $[\alpha]_D^{20} = -5.4°$ (c = 1, methanol). – UV (methanol), ^{1}H- and ^{13}C-NMR ($CDCl_3$): Tables 1 and 2. – MS (70 eV): relevant peaks at m/e = 652 (1%, M^+), 259 (44, triacetylribosyl$^+$), 137 (12, allopurinol$^+$ + 1), 43 (100, Ac^+).

$C_{27}H_{32}N_4O_{15}$ (652.6) Calcd. C 49.69 H 4.94 N 8.56
6b: Found C 49.65 H 5.01 N 8.48
7b: Found C 49.52 H 4.91 N 8.43

The middle zone similarly afforded 376 mg (12%) of *2,5-dihydro-2,5-bis(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one* (**7b**) as a foam of $[\alpha]_D^{20} = -30.5°$ (c = 1, methanol). – UV (methanol) and ^{1}H-NMR: Table 1. – MS (70 eV): practically identical to **6b**.

The slowest moving zone gave a syrupy mixture of the 1-, 2-, and 5-riboside triacetates **9b**, **10b**, and **11b** (900 mg, 25%); a separation was renounced due to their closely similar mobilities.

Free allopurinol ribosides

1,5-Dihydro-1,5-bis(β-D-ribofuranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one (**6c**): 850 mg (0.83 mmol) of hexabenzoate **6a** in 0.02 N methanolic sodium methoxide (100 ml) was kept for 15 h at ambient temperature and was subsequently de-ionized by stirring with a strongly acidic ion exchanger (Lewatit, H^+-form, Merck) for 30 min. Removal of the resin, washing with methanol, subsequent evaporation of the combined filtrates, and several co-evaporations from benzene/ethanol (1 : 1) left a crystalline residue, which was recrystallized from methanol: 287 mg (86%) as long staples; m. p. 148 – 149°C (after drying over P_2O_5 at 50°C), $[\alpha]_D^{20} = -47°$ (c = 0.6, methanol). – UV, ^{1}H- and ^{13}C-NMR: Tables 1 and 2. – MS (FD): m/e = 401 (100%, M^+ + 1).

$C_{15}H_{20}N_4O_9$ (400.3) Calcd. C 45.00 H 5.04 N 14.00
6c: Found C 44.86 H 4.96 N 14.02
7c: Found C 44.94 H 5.01 N 13.89

2,5-Dihydro-2,5-bis(β-D-ribofuranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one (**7c**): 570 mg (0.55 mmol) of **7a** was debenzoylated as described above to yield 60 mg (27%) of an amorphous product melting at 94–100°C; $[\alpha]_D^{25} = -51°$ (c = 1, methanol). – UV, ^{1}H- and ^{13}C-NMR: Tables 1 and 2.

1,5-Dihydro-1-(β-D-ribofuranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one (**9c**): 610 mg (1.05 mmol) of **9a** was debenzoylated with 0.02 N methanolic sodium methoxide (55 ml) at room temperature (2 h). After processing as described for **6c**, the residue obtained was recrystallized from hot methanol (10 ml): 190 mg (68%), m. p. 172–174°C, $[\alpha]_D^{25} = -70.2°$ (c = 0.53, methanol). UV, ^{1}H- and ^{13}C-NMR data cf. Tables 1 and 2.

The melting points given in the literature vary within an unusually wide range, i. e. 164°C[27], 171–173°C with subsequent resolidification and remelting at 205–206°C[28], 185–195°C (dec. after sintering at 120–125°C) for a hemihydrate[8a], 201–202°C[18,29], 211°C[25], and 271°C[29,30]. Our value (172–174°C) was found on several preparations of **9a** as well as on a sample[31] prepared via an independent route[28]. – The only available rotational value for **9a**, i. e. $[\alpha]_D^{25} = -71.9°$ (c = 1.3, water)[27], is in fair agreement with ours.

2,5-Dihydro-2-(β-D-ribofuranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one (**10c**): A solution of **10a** (410 mg, 0.71 mmol) in 0.02 N methanolic $NaOCH_3$ was stirred at ambient temperature for 2 h and subsequently de-ionized with a strongly acidic ion exchange resin (4 ml Lewatit, H^+-form, Merck). Removal of the resin and evaporation of the filtrate gave a residue, which crystallized after co-evaporations from benzene/methanol (1:1, 3 × 50 ml). Recrystallization from methanol/ethanol (1:1) afforded 103 mg (53%) of **10c**; m. p. 185°C (dec.), $[\alpha]_D^{25} = -79.4°$ (c = 0.6, methanol) and $-84.1°$ (c = 0.9, water).

The product was identical with respect to m. p., mixed m. p., rotation, and chromatographic behaviour in several solvent systems (C proved very effective for differentiation of the monoribosides **9c**, **10c**, and **11c**) with a sample[33] from another preparative route, for which m. p. 185–187°C (dec.) and $[\alpha]_D = -83.6°$ (water) was reported[30]. Similarly, the ^{1}H-NMR data ([D$_6$]DMSO) correlate well except for the chemical shift of the low field heterocyclic proton (s at δ = 8.96[30] versus 8.63 in Tab. 1); this discrepancy is clearly due to the fact that the former value stems from a product containing some acetic acid (≈0.1 molar equivalent, originating from the diethoxymethyl acetate used for its preparation), since addition of a drop of acetic acid to a DMSO-solution of **10c**, as prepared above, shifted the 8.63 signal to 8.86 ppm.

1,5-Dihydro-5-(β-D-ribofuranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one (**11c**)

a) *By de-O-benzoylation of* **11a**: 160 mg of **11a** were exposed to 0.02 N methanolic sodium methoxide (25 ml) for 2 h at ambient temperature and processed as usual (cf. **6c**): 65 mg (88%) of **11c**, m. p. 207–208°C, $[\alpha]_D^{25} = +18.4°$ (c = 0.38, methanol). – UV, ^{1}H- and ^{13}C-NMR: Tables 1 and 2. – MS (FD): m/e = 269 (100%, $M^+ + 1$), 268 (45, M^+).

$C_{10}H_{12}N_4O_5$ (268.2) Calcd. C 44.78 H 4.51 N 20.89 Found C 44.73 H 4.54 N 20.79

b) *By ribosylation of* **4** *with* **5b** *and ensuing de-O-acetylation:* 1.4 g (5.0 mmol) of **4** and 1.5 g of **5b** are reacted with $SnCl_4$ (0.4 ml) in dichloroethane as described above for the preparation of **6b** and **7b**, and processed analogously. The colorless foam thus obtained was subjected to treatment with satd. methanolic ammonia (24 h at 5°C). Evaporation to dryness in vacuo and trituration with methanol (10 ml) gradually induced crystallization: 170 mg (12%) of **11c**, crystallizing with one mol of acetamide; m. p. 205–206°C after sintering around 155°C, $[\alpha]_D^{20} = +23.3°$ (c = 0.82, water). – ^{1}H-NMR ([D$_6$]DMSO): δ-values analogous to the product obtained above (Table 1), yet with the additional signals for acetamide [δ = 1.81 (s, 3H, CH_3), ≈7.5 (m, 2H, NH_2)]. – MS (FD): m/e = 269 (100%, $M^+ + 1$), 268 (45, M^+).

$C_{10}H_{12}N_4O_5 \cdot CH_3CONH_2$ (327.3) Calcd. C 44.03 H 5.24 N 21.40
Found C 43.95 H 5.27 N 21.34

Methylated allopurinols

1,5-Dihydro-1,5-dimethyl-4H-pyrazolo[3,4-d]pyrimidin-4-one (**14**) *and its 2,5-dimethyl isomer* (**16**): To a solution of 2.8 g (20.6 mmol) of **1** in 2 N NaOH (30 ml) was added dropwise dimethyl sulfate (6.1 g, 48.6 mmol) with stirring which was continued for 15 h at ambient temperature. The precipitate formed was filtered off and recrystallized from ethanol: 310 mg (9%) of **16** as rod-like crystals; m. p. 296°C (lit. 293 – 295°C[22] and 295 – 198°C[24]), R_F = 0.13 (E), 0.32 (C), 0.55 (D). – ^{13}C-NMR: cf. Table 2.

Extraction of the filtrate with chloroform (3 × 100 ml; aqueous phase vide infra), drying (Na_2SO_4) of the combined extracts and removal of the solvent left a crystalline mixture of **14**, **16**, and another three UV-detectable (TLC) minor products in an approximate ratio of 2:1:1 (TLC in C, or E). Trituration with hot ethanol (15 ml) left the difficulty soluble **16** which was removed. Evaporation of the filtrate and recrystallization from n-butyl acetate gave 550 mg (16%) of **14** as needles of m. p. 193 – 195°C (lit. 193 – 195°C[21] and 191 – 195°C[24]); R_F = 0.24 (E), 0.58 (C), 0.75 (D). – ^{13}C-NMR cf. Table 2.

1-Methyl-3-(methylamino)-4-pyrazolecarboxamide (**18**): The aqueous phase remaining after chloroform extraction (vide supra) was now exhaustively extracted with chloroform (10 × 100 ml) to yield after evaporation of the extracts a residue consisting of an estimated (TLC in C) 3:3:1 mixture of **16**, **18**, and **12** aside 5 minor components. Removal of **16** by extraction with hot ethanol, separation of the extract by PLC with solvent system C, elution of the middle zone with ethanol, evaporation and recrystallization of the residue from ethanol afforded 158 mg (5%) of **18**, m. p. 189°C, R_F = 0.27 (E), 0.33 (D), 0.44 (C). – UV a) in 0.1 N HCl: λ_{max} (lg ε) = 232 (3.99), 270 (3.80), λ_{min} 252 nm (3.57); b) at pH 7.5: λ_{max} = 275 (3.74), λ_{min} = 247 (3.47); no change at pH 13. – ^{1}H-NMR ([D$_6$]DMSO): δ = 2.77 (d, *J* = 5.5 Hz, 3H, NH – CH_3), 3.67 (s, 3H, 1-CH_3), 5.78 (d, *J* = 5.5 Hz, 1H, NH), 6.90 (s, 2H, NH_2), 7.89 (s, 1H, 5-H). – MS (70 eV): *m/e* = 154 (67%, M^+).

$C_6H_{10}N_4O$ (154.2) Calcd. C 46.74 H 6.54 N 36.34
18: Found C 46.66 H 6.55 N 36.29
19: Found C 46.71 H 6.50 N 36.31

3-Amino-1,N-dimethyl-4-pyrazolecarboxamide (**19**)

a) *By treatment of* **16** *with alkali:* 390 mg of **16** were stirred in 2 N NaOH (5 ml) for 15 h at room temperature. Subsequent extraction of the mixture with chloroform (5 × 50 ml) and evaporation of the extracts gave 335 mg (92%) **19** as colorless crystals of m. p. 160 – 162°C; R_F = 0.21 (E), 0.31 (D), and 0.33 (C). – UV a) in 0.1 N HCl: λ_{max} (lg ε) = 261 (3.64), 228 (3.98), λ_{min} = 248 nm (3.58); b) at pH 7.5: λ_{max} = 259 (3.84), λ_{min} 242 (3.71), no change at pH 13. – ^{1}H-NMR ([D$_6$]DMSO): δ = 2.70 (d, *J* = 5 Hz, 3H, $CONCH_3$), 3.62 (s, 3H, 1-CH_3), 5.32 (s, 2H, NH_2), 7.65 (d, *J* = 5 Hz, 1H, NH), 7.83 (s, 1H, 5-H). – MS (70 eV): *m/e* = 154 (62%, M^+), 124 (100, $M^+ - NHCH_3$).

b) *From the allopurinol methylation mixture:* The fastet moving zone from the PSC separation (as described above for **18**) afforded on elution with acetone and evaporation of the eluate 160 mg (6%) of **19**, identical in all respects with the product described under a).

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[35] Merck Catalogue 1980, p. 289.
[36] *J. A. Montgomery* and *H. J. Thomas,* J. Org. Chem. **34**, 2646 (1969).
[37] A detailed assessment of chemical shifts of anomeric and heterocyclic protons in relation to the ribosylation pattern is contained in *E. Cuny,* Dissertation, Techn. Hochschule Darmstadt 1976.
[38] We are indebted to Dr. *U. Jahn,* Pharmacology Research Laboratory, Siegfried AG, Zofingen, Switzerland, for kindly performing these experiments.
[39] Grade 4 Å of 2 mm pearls (Merck, Darmstadt).

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