Synthesis of Pyrrolo[2,3-*d*]pyrimidine Ribosides and their Potential in Chemotherapeutics

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**Dedicated to Professor K. Gewald,
Technical University of Dresden on the occasion of his 60th birthday**

The synthesis of a number of 5,6-dimethylpyrrolo[2,3-*d*]pyrimidines substituted in position 7 with ribose, deoxyribose, respectively and their acyclic analogues is described and their potential in chemotherapeutics was tested. None of the compounds showed remarkable biological effects.

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Introduction.

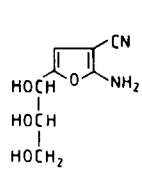
Selected *N*-7-phenyl-substituted pyrrolo[2,3-*d*]pyrimidines (*i.e.* 7- deazapurines) have been observed to show antiphlogistic and anticonvulsant effects [1,2]. Even their precursors, the 2-aminopyrrole-3-carbonitriles, exhibit biological activities such as inhibition of 5-lipoxygenase and inhibition of chemiluminescence [3].

Recently we reported the possibility of synthesizing 7-unsubstituted pyrrolo[2,3-*d*]pyrimidines [4]. Now we have been able to produce both 7-substituted and unsubstituted pyrrolo[2,3-*d*]pyrimidines [8] using the one method. Starting with α-hydroxyketones, primary amines and malononitrile [1], the initial intermediates were α-aminoketones, which were, without isolation, cyclized to the 2-aminopyrrole-3-carbonitriles. The reaction was completed by ring closure with formic acid derivatives, thus furnished the desired pyrrolopyrimidines. Only a few primary amines, *e.g.* anilines with bulky or electron withdrawing groups in the ortho position, are unsuitable for this synthetic route. This paper reports the use of amino sugars and their derivatives as the amine components in the above synthetic pathway. The resulting heterocycles from such reactions are of interest as possible analogs of the naturally occuring antibiotics toyocamycin and tubercidin [5].

Results and Discussion.

According to our previously reported method [4] malononitrile and an amine are reacted to give a pyrrole, under these conditions ribosylamine [6] was used as the amine component however no pyrrole derivative could be detected. Only the furan **1** has been produced [7]. In the next step the reactions of 1-aminopropan-2-ol (**2**) and 3-aminopropane-1,2-diol (**3**) were tested as amine components in order to get pyrrolo[2,3-*d*]pyrimidines with a partial glycoside moiety. In both cases it was possible to insert **2** and **3** respectively, to give the pyrrole derivatives **4** and **5a** in good yields. But only **4** could be directly cyclized with formamide [8] to give **6**. With **5a** the annelation of the pyrimidine ring was achieved according to a method described by Taylor [9] which gave **7a** in three steps. By the reaction of **5a** with triethylorthoformate the amidine **5c** is formed *via* the iminoether **5b**,**5c** cyclized with alkali to the pyrrolo[2,3-*d*]pyrimidine **7b**. Spectral data did not show the presence of the dihydroxypropyl moiety presumably as a result of it also having reacted with triethylorthoformate. The cleavage of the ester proceeded by heating **7b** in methanolic hydrogen chloride solution yielding **7a**. Since all efforts to introduce the sugar moiety in the course of pyrrole synthesis had hitherto failed, we attempted to condense deoxyribose directly with the pyrrole **9** [19] according to [12a]. Although no visible solubility of either deoxyribose or the pyrrole could be detected under these reaction conditions, the *N*-glycoside **10** was obtained in 70% yield. Under milder conditions, as described above, 95% yield could be reached with the pyrrole being nearly analytical pure. The conversion was also successful with ribose, yielding the oily product **11**. The amines **12**, **14** were also reacted with deoxyribose, the products **13** and **15** resulting. (Schematic representations are given in Table 1). Because of the previously observed lability of the furan **14** [21], it is not surprising that the *O*-riboside **15** was obtained. Recently Pedersen *et al.* [12b] reported also condensation reactions of unprotected deoxyribose/ribose with various heterocyclic systems with another method. Hardegger condensed aniline (**17**) with deoxyribose to yield **18** [11], the same compound was obtained under our conditions. However the 2-amino-3-cyano-4,6-diphenylpyridine (**19**) [22], as an example of an enaminonitrile system in a six-ring-heterocycle, did not show any conversion with the sugar, similarly **16** did not react. It was also disappointing that Davoll's pyrimidine **20** [23], a synthon for pyrrolo[2,3-*d*]pyrimidine synthesis, did not show any readiness to react.

The absolute configuration and constitution of **10**, **11**, **13** and **15** was determined in a similar manner for these compounds. Consideration of **10** is given below as an example. Because of the high field shift of C-4' to 66 ppm in



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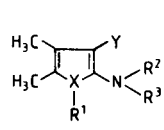
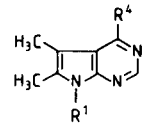
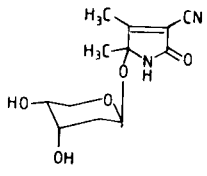


4, 5, 9
10–14, 16



6, 7, 21
25, 27–30



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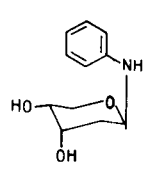

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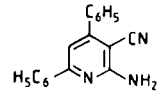
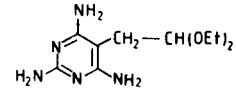


19



20

Table 1

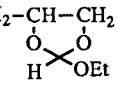
4a,b

a: $R^1 = -CH_2-CHOH-CH_3$
b: $R^1 = -CH_2-CH=CH_2$
a,b:
$R^2, R^3 = -H$
X = >N, Y = –CN

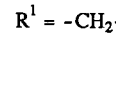
5a

$R^1 = -CH_2-CHOH-CH_2OH$
$R^2, R^3 = -H$
X = >N, Y = –CN

5b

$R^1 =$ 
$R^2, R^3 =$ =C–OEt
X = >N, Y = –CN

5c

$R^1 =$ 
$R^2, R^3 =$ =CH–NH_2
X = >N, Y = –CN

6

R^1 = s. **4**
$R^4 = -NH_2$

7a,c

a,c, R^1 = s. **5a**
a, $R^4 = -NH_2$
c, $R^4 = -OH$

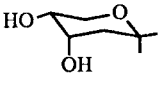
7b

R^1 = s. **5b**
$R^4 = -NH_2$

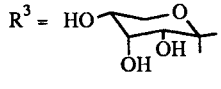
9

$R^1 = -H$
$R^2, R^3 = -H$
X = >N

10

$R^1 = -H$
$R^2 = -H$
$R^3 =$ 
X = >N, Y = –CN

11

$R^1 = -H$
$R^2 = -H$
$R^3 =$ 
X = >N, Y = –CN

12

$R^2, R^3 = -H$
X = >S, Y = –CN

13

$R^2 = -H$
R^3 = s. **10**
X = >S, Y = –CN

14

$R^2, R^3 = -H$
X = >O, Y = –CN

16

$R^1, R^2, R^3 = -H$
X = >S, Y = $-CONH_2$

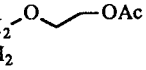
21a,b

$R^1 = -H$
a: $R^4 = -NH_2$
b: $R^4 = -OH$

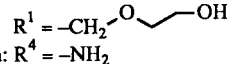
25a,b

$R^1 = -CH_2-CH=CH_2$
a: $R^4 = -NH_2$
b: $R^4 = -OH$

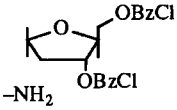
27a,b

$R^1 =$ 
a: $R^4 = -NH_2$
b: $R^4 = -OH$

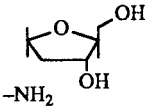
28a,b

$R^1 =$ 
a: $R^4 = -NH_2$
b: $R^4 = -OH$

29

$R^1 =$ 
$R^4 = -NH_2$

30

$R^1 =$ 
$R^4 = -NH_2$

the ^{13}C-nmr-spectrum in comparison with literature data [24a], the pyranose form was assigned. The triplet at 4.72 ppm with J = 5.5 Hz can be regarded as evidence of a β-glycosidic linkage. Under different reaction conditions Dimroth rearrangement failed to convert the exocyclic sugar moiety to N-1. As a consequence of these results, the sugar moiety must be introduced in the complete 7-unsubstituted pyrrolo[2,3-*d*]pyrimidine skeleton. Model experi-

ments regarding nucleophilic substitution show in accordance with recently published work [25a] that after activation with sodium hydride in dimethyl sulfoxide N-7 is the main target for alkylation. The reaction of 1-halosugars with nucleobases being also a nucleophilic substitution, the attack of the sugar should proceed in parallel to the *N*-alkylation reaction.

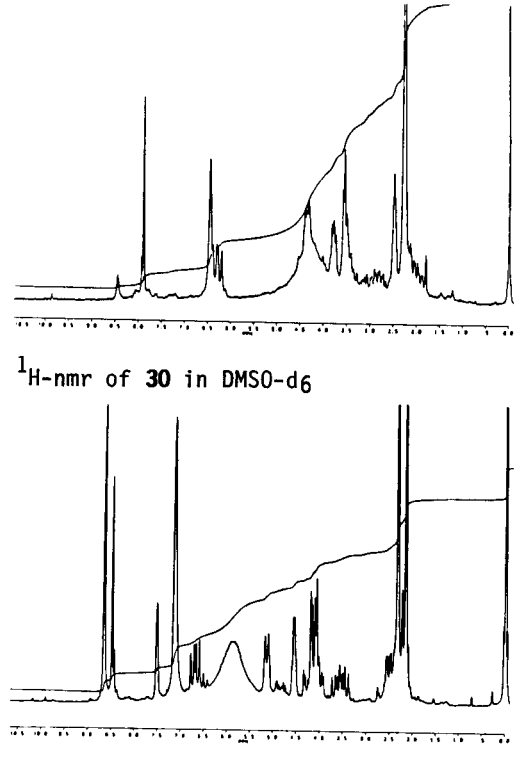
Table 2
Cytotoxic/antiviral Activity

Compound	HSV I		HSV II	
	500 µg/ml	50 µg/ml	500 µg/ml	50 µg/ml
5c	-/-	-/-	-/-	-/-
6	xxxx/-	xx/-	xxxx/-	xx/-
7a	-/-	-/-	-/-	-/-
7b	-/xxx	-/-	-/xxx	-/-
7c	-/x	-/-	-/x	-/-
10	-/x	-/-	-/x	-/-
11	-/-	-/-	-/-	-/-
21a	xxx/-	-/-	xxx/-	-/-
21b	xxx/-	x/-	xxx/-	x/-
25a	xxxx/-	-/x	xxxx/-	-/x
25b	xxxx/-	xx/-	xxxx/-	xx/-
28a	-/-	-/-	-/-	-/-
30	-/x	-/-	-/x	-/-

Cytotoxicity: % inhibition of cell growth. Antiviral activity: % reduction of plaques.

- : no effect
x : 25%
xx : 50%
xxx : 75%
xxxx : 100%

First efforts in this direction were undertaken with the glycerine derivatives **22-24**: experiments with epichlorohydrin (**22**) in propanol/piperidine, or with 1-tosylisopropylideneglycerol (**23**) in dimethyl sulfoxide, in the presence of sodium hydride failed. In another attempt to obtain **7a** and **7c** we tried to oxidize the 7-allylpyrrolopyrimidines **25a** and **25b** with potassium permanganate according to the method of Skaric [27], but this again prove unsuccessful. The unprotected glycerol-α-chlorohydrin (**24**) however furnished the desired products **7a** and **7c** using the method described by LaMontagne [26a]. The same procedure used for synthesizing **7a,c** is also applicable to introduce the 2-hydroxy-ethoxy-moiety **26** [28] into the molecule. By this method the acyclovir-analogs **27** and **28** of the 7-deazapurines **21a** and **21b** can be synthesized in 46% yield. Recently Townsend *et al.* described 2,4-disubstituted derivatives of this type [25a]. As complete sugar component the 1-chloro-3,5-di-*p*-chlorobenzoyldeoxyribose was reacted with the 4-aminopyrrolo[2,3-*d*]pyrimidine **21a**. Removal of the protecting groups in **29** furnished **30** in good yield. Successful glycosylations of pyrrolo[2,3-*d*]-pyrimidines have repeatedly been reported, using various conditions, *e.g.* dimethylformamide/sodium hydride [29a], phase-transfer conditions [29b] etc. It should be mentioned that 4-chloropyrrolo[2,3-*d*]pyrimidines with a methylthio-functionality in position 2 are selected for glycosylation to avoid the formation of regioisomers. That means two further steps are necessary: first removal of the activating group in position 2 and second, substitution of the chloro atom in position 4. Using our method and/or compound **21a** the direct conversion of the 4-amino derivative is possible. Beside this, no regioisomers and no α-anomer are detectable in **30**, Elucidation of the nature and configuration of **30**, again relies on spectral data. A signal at 6.33 ppm for the anomeric proton and the difference of 0.54 ppm between H-3′ and H-4′ are considered as strong evidence of the furanose structure [24a]. Confirmation of this is found in the ^{13}C-nmr-spectrum, where the doublet for C-4′ lies in the 87.23 ppm region. The differentiation between α- and β-linked nucleosides is possible by comparison of the chemical shifts of H-3′, H-4′ and H-5′ [24b, 30-32]. The peak width of the multiplet of the 2′protons, in some references [24a, 33] observed as a distinctive characteristic, cannot be used in this case because the H-2′ multiplet is overlapped by the methyl-signals of the pyrrolo[2,3-*d*]pyrimidine. In the course of these nmr studies for nucleosides we have found, that all the spectra previously



^{1}H-nmr of **30** in DMSO-d$_6$

Figure 1. ^{1}H-nmr of **30** in pyridine-d$_5$

reported were be recorded with dimethyl sulfoxide-d_6 or deuterium oxide as solvent in spite of the fact that overlapping of signals made the interpretation difficult. In particular the water peak is a sometimes inevitable disturbing factor. Therefore it is astonishing that to our knowledge pyridine-d_5 has not been used for nucleoside studies in this field. For comparison Figure 1 shows the ^{1}H-nmr-spectra of **30** in dimethylsulfoxide-d_6 and pyrimidine-d_5 as solvents. In the latter all signals are shifted downfield and no disturbing peaks of the solvent or of water are in the important high field region. Splitting pattern and coupling constants are more easily recognized and allow for a better interpretation.

Biological Evaluations.

Compounds **7a** and **7c** were evaluated for activity against phytopathogenic germs, but no positive results were forthcoming. In a further study compounds **7a**, **7b**, **10**, **13**, **25a**, **25b**, **28a** and **30** were evaluated for activity against *staphylococcus aureus, pseudomonas aeruginosa* and *candida albicans* by using agar diffusion test system. Beside compound **25a**, which showed antibacterial activity at 20 mg/ml and antifungal activity at 2 mg/ml, all compounds gave negative results. Sangivamycin, Toyocamycin and Tubercidin are reported to have antiviral, antineoplastic and antiparastic activity yet their toxicity has forbidden clinical trails. In recent years however a renewed interest in these antibiotics has been registered [34]. Consequently a number of our compounds were evaluated for activity against HSV-1 and HSV-2 by using the plaque reduction assay. Cytotoxicity of each compound was also examined in mouse embryo cells. Table 2 shows that nearly all compounds were inactive.

Nonetheless some results should be mentioned. In particular it is of interest that the 7-unsubstituted pyrrolo-[2,3-*d*]pyrimidines **21a** and **21b** showed a relatively high cytotoxicity which disappeared after conversion to the 2'-deoxy derivative **30**, or to the 7-[(2-hydroxyethoxy)-methyl]-derivative **28a** or also to the glycerol derivative **7a**. It seems remarkable however that after introduction of an allyl group in position 7 (**25a,b**) the cytotoxicity is retained. The same effect was shown by other substituents in position 7, like phenyl or saturated alkyl (not reported in this paper). It may then be postulated that increasing lipophilicity in the molecule produces such cytotoxic effects. It is therefore astonishing that only **7b** shows distinct antiviral effects in high dose (500 μg/ml). Compounds **25b** and **28a** were further subjected to screening tests for cytostatics. In the proliferation assay (MTT-reduction) both compounds showed no activity.

EXPERIMENTAL

Melting points (°C) were determined in open capillaries and are uncorrected. Infrared discs spectra were recorded in potassium bromide disks on a Perkin-Elmer FT-IR-spectrometer 1750. The ^{1}H- and ^{13}C-nmr-spectra were taken on a Bruker AC-80 with TMS as internal standard, δ [ppm], J = Hz. DMSO-d_6 or pyridine-d_5 were used as solvents.

2-Amino-1-(2-hydroxypropyl)-4,5-dimethylpyrrole-3-carbonitrile (**4a**) and 5,6-Dimethyl-7-(2-hydroxypropyl)-pyrrolo[2,3-*d*]pyrimidin-4-amine (**6**).

A mixture of 7.5 g (0.1 mole) of 1-aminopropane-2-ol (**2**), 8.8 g (0.1 mole) of acetoin and 50 mg of *p*-toluenesulphonic acid in dry benzene was heated with the aid of a Dean-Stark trap until 1.8 ml of water was separated. After cooling 6.6 g (0.1 mole) of malononitrile and 1 ml of piperidine were added and the mixture refluxed for 2 hours. On cooling the solvent was removed on a rotary evaporator and the residue crystallized from the remaining oil and without purification treated with formamide see (**25a**), yield 8.7 g (79%), mp, 234°; ^{1}H-nmr spectrum: δ 1.0 (d, 3H, CH_3-CHOH), 2.3 (s, 6H, 4-CH_3, 5-CH_3), 4.0 (br, 3H, CH-OH, CH_2N-), 4.8 (br, 1H, OH), 6.4 (br, 2H, NH_2), 8.05 (s, 1H, 2-H).

Anal. Calcd. for $C_{11}H_{16}N_4O$ (220.27): C, 59.98; H, 7.32; N, 25.44. Found: C, 59.88; H, 7.36; N, 25.64.

2-Amino-1-(2,3-dihydroxypropyl)-4,5-dimethylpyrrole-3-carbonitrile (**5a**).

A method similar to **4a** using 9.2 g (0.1 mole) of 3-amino-1,2-propanediol (**3**) and 8.8 g (0.1 mole) of acetoin yielded 13.8 g (66%) of **5a** as a viscous brown oil, $C_{10}H_{15}N_3O_2$ (209.25).

4,5-Dimethyl-2-ethoxymethyleneamino-1-(2,3-*O*-ethoxymethylene-2,3-dihydroxypropyl)pyrrole-3-carbonitrile (**5b**).

A solution of 6.5 g (31 mmoles) of **5a**, 75 ml of triethylorthoformate and 50 mg of *p*-toluenesulfonic acid in ethanol was refluxed for 3 hours. The reaction mixture was evaporated *in vacuo* and the residue was triturated with a few ml of ethanol. Filtration of the precipitate and recrystallization from ethanol yielded 7.2 g (73%) of **5b** mp, 95°, $C_{16}H_{23}N_3O_4$ (321.38); ^{1}H-nmr: δ 1.07 (t, 3H, OOCH-OCH$_2$-CH_3), 1.28 (t, 3H, NCH-OCH$_2$-CH_3), 1.90 (s, 3H, 5-CH_3), 2.04 (s, 3H, 4CH_3), 3.36 (q, 2H, OOCH-OC-H_2-CH_3), 3.49-4.23 (m, 5H, 4'-H, 5'H, N-CH_2-bridge), 4.16 (q, 2H, NCH-OCH_2-CH_3), 5.59 (s, 1H, 2'-H), 8.01 (s, 1H, NC*H*-OCH$_2$-CH_3).

2-Aminomethyleneamino-4,5-dimethyl-1-(2,3-*O*-ethoxymethylene-2,3-dihydroxypropyl)pyrrole-3-carbonitrile (**5c**).

Ammonia gas was bubbled through a solution of 1.0 g (3.8 mmoles) of **5b** in 40 ml of methanol for 30 minutes. After standing overnight the solvent was removed under reduced pressure leaving a final volume of 5 ml. The residue was allowed to stand overnight at -20° and the precipitate was collected by filtration, yield 0.23 g (21%), mp: 100°, $C_{14}H_{20}N_4O_3$ (292.34); ^{1}H-nmr: δ 1.12 (t, 3H, OCH$_2$-CH_3), 1.94 (s, 3H, 5-CH_3), 2.08 (s, 3H, 4-CH_3), 3.50 (q, 2H, OCH_2-CH_3), 3.66-4.33 (m, 5H, 4'-H, 5'-H, CH_2-bridge), 5.79 (s, 1H, 2'-H), 7.19 (s, 2H, NH_2), 7.96 (t, 1H, N=C*H*-N½).

5,6-Dimethyl-7-(2,3-*O*-ethoxy-4-methylene-2,3-dihydroxypropyl)-pyrrolo[2,3-*d*]pyrimidin-4-amine (**7b**).

To a solution of **5c** in methanol, saturated with ammonia, 0.7 g of sodium hydroxide was added the mixture was stirred for 6 hours. After concentration of the reaction mixture *in vacuo* the

residual of approximately solution 10 ml was left overnight at -20°. The resultant precipitate was collected by filtration and recrystallized from ethanol, yield 0.87 g (78%), mp 171°, ^{1}H-nmr: δ 1.11 (t, 3H, CH_2-C H_3), 2.29 (s, 6H, 6-CH_3, 5-CH_3), 3.50 (q, 2H, CH_2-CH_3), 3.79 (q, 1H, 4'-H), 4.05-4.50 (m, 4H, 5'H, CH_2-bridge), 5.79 (s, 1H, OOC*H*-CH_2CH_3), 6.37 (s, 2H, NH_2), 7.96 (s, 1H, 2-H).

Anal. Calcd. for $C_{14}H_{20}N_4O_3$, (292.34): C, 57.25; H, 6.90; N, 19.16. Found: C, 57.58; H, 6.99; N, 19.27.

7-(2,3-Dihydroxypropyl)pyrrolo[2,3-*d*]pyrimidin-4-amine (**7a**). Method A.

A solution of 0.5 g (1.7 mmoles) of **7b** in 30 ml of methanol and 20 ml of methanol, saturated with hydrogen chloride gas, was refluxed for 1.5 hours. The solvent was evaporated *in vacuo*, the residue treated with methanol. The filtrate was evaporated to dryness and the residue recrystallized from methanol, yield 0.3 g (64%), mp 246°. To receive the free base of **7a** the hydrochloride was dissolved in water and treated with diluted sodium hydroxide solution. The precipitate was collected by filtration and washed with cold ethanol and ether, yield 0.15 g (37% referred to **5c**), mp 196-197°.

Method B.

To an ice cooled mixture of 10 ml of absolute dimethyl sulfoxide and 0.33 g (11 mmoles) of sodium hydride (80%) was added with stirring 1.62 g (10 mmoles) of 4-amino-5,6-dimethyl-7(*H*)-pyrrolo[2,3-*d*]pyrimidine (**21a**) [4]. After gas evolution had finished, 1.22 g (11 mmoles) of 1-chloro-2,3-propanediol (**24**) was added and the mixture stirred for 2 hours at room temperature. After pouring on ice the mixture was left overnight at 4° and the formed precipitate was collected by filtration. Purification by recrystallization from methanol yielded 1.23 g (52%), mp 196-197°; ^{1}H-nmr; δ 2.28 (s, 6H, 6-CH_3, 5-CH_3), 3.37 (m, 2H, 3'-H), 3.80 (m, 1H, 2'-H), 4.04 (m, 2H, 1'-H), 4.87 (m, 2H, 2'-OH, 3'-OH), 6.36 (s, 2H, NH_2), 7.95 (s, 1H, 2-H); ^{13}C-nmr: δ 9.54 (q, 6-CH_3, J = 131), 10.58 (q, 5-CH_3, J = 131), 44.74 (t, 1'-C, J = 146), 63.49 (t, 3'-C, J = 146), 70.78 (d, 2'-C, J = 150), 102.20 (s, 5-C), 103.97 (s, 4α-C), 129.76 (s, 6-C), 150.03 (s, 7α-C), 150.21 (d, 2-C, J = 212), 157.07 (s, 4-C).

Anal. Calcd. for $C_{11}H_{16}N_4O_2$ (236.28): C, 55.92; H, 6.83; N, 23.71. Found: C, 56.17; H, 6.72; N, 23.71.

7-(2,3-Dihydroxypropyl)-5,6-dimethylpyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**7c**).

In a method similar to **7a**, method B, 1.63 g (10 mmoles) of 5,6-dimethyl-7(*H*)-pyrrolo[2,3-*d*]pyrimidine-4(3-*H*)-one (**21b**) [4] was reacted with 1.22 g (11 mmoles) of 1-chloro-2,3-propanediol (**24**). The mixture was poured on ice and extracted with 1-butanol. After removal of the solvent *in vacuo*, **7c** crystallized spontaneously from the resulting oil. The product was washed with cold ethanol and ether, yield 0.63 g (25%), mp 254°; ^{1}H-nmr: δ 2.18 (s, 3H, 6-CH_3), 2.22 (s, 3H, 5-CH_3), 3.13-3.35 (m, 2H, 3'-H), 3.43-3.72 (s, 2H, 1'-H), 4.10 (m, 1H, 2'-H), 4.57 (t, 1H, 3'-OH, J = 5.3), 4.77 (d, 1H, 2'-H, J = 5.5), 7.65 (s, 1H, 2-H), 11.05 (s, 1H, NH).

Anal. Calcd. for $C_{11}H_{15}N_3O_3$ (237.26): C, 55.68; H, 6.37; N, 17.71. Found: C, 55.79; H, 6.40; N, 17.75.

2-(2-Deoxy-*d*-erythropentopyranosylamino)-4,5-dimethylpyrrole-3-carbonitrile (**10**).

A mixture of 1.0 g (7.4 mmoles) of 2-amino-4,5-dimethylpyrrolo-3-carbonitrile (**9**) [18] and 1.0 g (7.5 mmoles) of 2-deoxyribose was triturated well in a mortar. The mixture was suspended in a solution of 50 ml of absolute toluene and 0.5 ml of acetic acid and then vigorously stirred for 2 hours at room temperature. The residue was collected by filtration and recrystallized from methanol, yield 1.76 g (95%), mp 18°; ^{1}H-nmr: δ 1.96-2.03 (m, 2H, 2'-H), 1.84 (s, 3H, 5-CH_3), 1.95 (s, 3H, 4-CH_3), 3.34-3.91 (m, 4H, 3'-H, 4'-H, 5'-H), 4.50 (m, 1H, 5'-OH), 4.72 (t, 1H, 1'-H, J = 5.5), 4.84 (m, 1H, 3'-OH), 6.58 (d, 1H, NH), 10.08 (s, 1H, 1-NH); ^{13}C-nmr: δ 9.12 (q, 5-CH_3, J = 133), 9.97 (q, 4-CH_3, J = 133), 34.03 (t, 2'-C, J = 135), 63.74 (t, 5'-C, J = 145), 72.81 (s, 3-C), 79.82 (d, 1'-C, J = 162), 111.68 (s, 4-C), 116.29 (s, 5-C), 118.08 (s, CN), 143.47 (s, 2-C).

Anal. Calcd. for $C_{12}H_{17}N_3O_3$ (251.29): C, 57.36; H, 6.82; N, 16.72. Found: C, 57.61; H, 6.74; N, 16.83.

2-(*d*-Erythropentopyranosylamino)-4,5-dimethylpyrrole-3-carbonitrile (**11**).

In a method similar to **10** 1.0 g (7.4 mmoles) of 2-amino-4,5-dimethylpyrrolo-3-carbonitrile (**9**) [19] was reacted with 1.13 g (7.5 mmoles) of ribose to yield 0.83 g (42%) of **11**, mp 100-113°, $C_{12}H_{17}N_3O_4$ (267.28); ^{1}H-nmr: δ 1.77 (s, 3H, 5-CH_3), 1.85 (s, 3H, 4-CH_3), 3.06-3.52 (m, 5H, 2'-H, 3'-H, 4'-H, 5'-H), 4.5 (d, 1H, 1'-H, J = 8.3), 4.48-4.68 (m, 3H, 2'-OH, 3'-OH, 4'-OH), 6.05 (d, 1H, NH, J = 9), 9.67 (s, 1H, 1-NH).

2-(2-Deoxy-*d*-erythropentopyranosyl)amino-4,5-dimethylthiophene-3-carbonitrile (**13**).

A mixture of 14 g (7.4 mmoles) of **12** [19] and 1.0 g (7.5 mmoles) of 2-deoxyribose was triturated and then suspended in 50 ml of absolute toluene. After addition of 0.5 ml of acetic acid the suspension was heated with stirring to 80° for 20 minutes. After cooling the precipitate was collected by filtration and washed with toluene, yield 1.66 g (84%), mp 162°; ms: M^+ 268; ^{1}H-nmr: δ 1.82 (m, 2H, 2'-H), 1.99 (s, 3H, 5-CH_3), 2.13 (s, 3H, 4-CH_3), 3.28-3.92 (m, 4H, 3'-H, 4'-H, 5'-H), 4.53 (m, 1H, 4'-OH), 4.65 (t, 1H, 1'-H, J = 5.25), 4.95 (d, 1H, 3'-OH, J = 5.5), 7.84 (d, 1H, NH, J = 8.0); ^{13}C-nmr: δ 11.86 (q, 5-CH_3, J = 138), 12.10 (q, 4-CH_3, J = 138), 33.71 (t, 2'-C, J = 125), 64.17 (t, 5'-C, J = 150), 66.24 (d, 4'-C, J = 150), 67.27 (d, 3'-C, J = 138), 81.29 (d, 1'-C, J = 155), 87.35 (s, 3-C), 116.0 (s, 4-C), 116.54 (s, CN), 128.92 (s, 5-C), 159.09 (s, 2-C).

Anal. Calcd. for $C_{12}H_{16}N_2O_3S$ (268.33): C, 53.71; H, 6.01; N, 10.44. Found: C, 53.64; H, 6.25; N, 9.72.

7-Allyl-5,6-dimethylpyrrolo[2,3-*d*]pyrimidin-4-amine (**25a**).

A mixture of 44.0 g (0.5 mole) of acetoin, 28.5 g (0.5 mole) of allylamine and 50 mg of *p*-toluenesulfonic acid was refluxed with the aid of a Dean-Stark trap. When 9 ml of water were collected, the mixture was cooled and 33.0 g (0.5 mole) of malononitrile were added. After additional refluxing for a short time the solvent was removed under reduced pressure. 17.5 g (0.1 mole) of the resultant oil was refluxed in a mixture of 150 ml of formamide, 50 ml of dimethylformamide and 20 ml of formic acid (85%) for 6 hours. While standing at 4° a precipitate formed, which was collected by filtration. For purification the crude product was dissolved in water and the solution was neutralized with a sodium hydroxide solution (10%). The precipitate was collected by filtration, yield 10.5 g (52%), mp 152°, $C_{11}H_{14}N_4$ (202.26); ^{1}H-nmr: δ 2.19 (s, 3H, 6-CH_3), 2.29 (s, 3H, 5-CH_3), 4.44-4.92 (m, 4H, 1'-H, 3'-H), 5.51-5.98 (m, 1H, 2'-H), 6.19 (s, 2H, NH_2), 7.70 (s,

1H, 2-H).

7-Allyl-5,6-dimethylpyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**25b**).

A mixture of 44.0 g (0.5 mole) of acetoin, 28.5 g (0.5 mole) of allylamine and 33.0 g (0.5 mole) of malononitrile were reacted as described for **25a**; 17.5 g (0.1 mole) of the resulting oil was refluxed for 5 hours in formic acid (85%). After cooling water was added up to a volume of 200 ml and the mixture was left at 4° for 2 hours. The precipitate was cooled by filtration, yield 10.0 g (49%), mp 238° $C_{11}H_{13}N_3O$ (203.24); ^{1}H-nmr: δ 2.16 (s, 3H, 6-CH_3), 2.24 (s, 3H, 5-CH_3), 4.5-5.12 (m, 4H, 1'-H, 2'-H), 7.7 (s, 1H, 2'-H), 11.35 (s, 1H, 3-NH).

7[(2-Acetoxyethoxy)methyl]-5,6-dimethylpyrrolo[2,3-*d*]pyrimidin-4-amine (**27a**).

Using a method similar to **7a**, method B, 1.62 g (10 mmoles) of **21a** [4] was converted with 1.68 g (11 mmoles) of **26** [26]. The reaction mixture was poured on ice and was extracted with ethyl acetate. The solvent was removed *in vacuo* and the remaining oil treated with ethylacetate and left overnight at -20°. The precipitate was collected by filtration. By concentrating the solvent, further product was obtained, overall yield 2.17 g (78%), mp 148°; ^{1}H-nmr: δ 1.96 (s, 3H, CO-CH_3), 2.28 (s, 6H, 6-CH_3, 5-CH_3), 3.44-4.19 (m, 4H, CH_2-CH_2), 5.51 (s, 2H, O-CH_2N), 6.44 (s, 2H, NH_2), 7.99 (s, 1H, 2-H).

Anal. Calcd. for $C_{13}H_{18}N_4O_3$ (278.30): C, 56.10; H, 6.52; N, 20.13. Found: C, 56.14; H, 6.60; N, 20.25.

7-[(2-Hydroxyethoxy)methyl]-5,6-dimethylpyrrolo[2,3-*d*]pyrimidin-4-amine (**28a**).

A solution of 0.7 g (2.5 mmoles) of **27a** in absolute methanol was prepared, 0.2 g of sodium methylate was added and the mixture left overnight. After neutralization with methanol, saturation with hydrogen chloride gas, and filtration, the filtrate was concentrated to about 5 ml. The precipitate was collected by filtration and recrystallized from methanol, yield 0.27 g (46%), mp: 249°, $C_{11}H_{16}N_4O_2$ (236.27); ^{1}H-nmr: δ 2.28 (s, 6H, 6-CH_3, 5-CH_3), 3.35 (m, 4H, CH_2-CH_2), 5.50 (s, 2H, O-CH_2-N), 6.42 (s, 2H, NH_2), 8.20 (s, 1H, 2-H).

7-[2-Deoxy-3,5-di-*O*-(*p*-chlorobenzoyl)-β-*d*-erythropentofuranosyl]-5,6-dimethylpyrrolo[2,3-*d*]pyrimidin-4-amine (**29**).

In a method similar to **7a**, method B, 1.62 g (10 mmoles) of 4-amino-5,6-dimethyl-7(*H*)-pyrrolo[2,3-*d*]pyrimidine **21a** [4] was reacted with 4.72 g (11 mmoles) of 3,5-di-*p*-chlorobenzoyl-1-chloro-2-deoxyribose. The precipitate was collected by filtration and well washed with water. Purification by column chromatography (silica, Fa, Merck, 0.2-0.5 mm), solvent ethyl acetate, yield 5.06 g (91%), mp 105-150°, $C_{27}H_{27}N_4O_5$ (555.42); ^{1}H-nmr: δ 1.87-2.71 (m, 2H, 2'-H), 2.26 (s, 3H, 6-CH_3), 2.31 (s, 3H, 5-CH_3), 4.36-4.68 (m, 3H, 5'-H, 4'-H), 5.81 (m, 1H, 3'-H), 6.44 (s, 2H, NH_2), 6.50 (t, 1H, 1'-H, J = 6.75), 7.45-8.05 (m, 8H, aromat), 8.10 (s, 1H, 2-H).

7-(2-Deoxy-β-*d*-erythropentofuranosyl)-5,6-dimethylpyrrolo[2,3-*d*]-pyrimidin-4-amine (**30**).

To a solution of 0.1 g (1.9 mmoles) of sodium methylate in 80 ml of absolute methanol, 1.0 g (1.8 mmoles) of **29** was added. The mixture was stirred for 4 hours, concentrated to about 25 ml of brought to *p*H 6 with ion-exchange resin (strong acidic, DOWEX 50Wx8, Aldrich). The ion exchange resin and the precipitated *p*-chloromethyl benzoate ester were filtered off and the filtrate was kept overnight at 4° followed by renewed filtration. The filtrate was twice refluxed for 30 minutes with active charcoal and was filtered while still hot. The solution was then evaporated to dryness and the residue recrystallized from methanol, yield 0.30 g (66%), mp 239°; ^{1}H-nmr (pyridine-d_5): δ 2.1-2.65 (m, 2H, 2'-H), 2.19 (s, 3H, 6-CH_3), 2.37 (s, 3H, 5-CH_3), 3.60 (m, 1H, 5'-OH), 4.17 (m, 2H, 4'-OH, 5'-OH), 4.60 (m, 1H, 4'-H), 5.18 (m, 1H, 3'-H), 6.75 (dd, 1H, 1'-H, J_1 = 6, J R_2 = 9.5), 8.54 (s, 1H, 2-H); ^{13}C-nmr: δ 9.90 (q, 6-CH_3), 10.38 (q, 5-CH_3), 38.36 (t, 2'-C), 62.18 (t, 5'-C), 71.18 (d, 3'-C), 83.71 (d, 1'-C), 87.23 (d, 4'-C), 102.91 (s, 5-C), 105.62 (s, 4α-C), 128.41 (s, 7α-C), 149.98 (d, 2-C), 157.17 (s, 4-C).

Anal. Calcd. for $C_{13}H_{18}N_4O_3$ (278.31): C, 56.10; H, 6.52; N, 20.13. Found: C, 56.23; H, 6.58; N, 19.99.

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REFERENCES AND NOTES

[1] Troponwerke, H. J. Roth, K. Eger, S. Issa and H. Jacobi, D.O.S. 2,818,676, 27 April, 1978; *Chem. Abstr.*, **92**, P 58818p (1980).

[2] Troponwerke, K. Eger, R. Fruchtmann, H. Hartmann, H. Jacobi, S. Raddatz and H. J. Roth, D.O.S. DE 3,145,287 14 Nov. 1981; *Chem. Abstr.*, **99**, P 5378e (1983).

[3] D. Steinhilber, K. Schmidt, K. Eger and H. J. Roth, *Pharm. Res*, **3**, 271 (1986).

[4] H. Pichler, G. Folkers, H. J. Roth and K. Eger, *Liebigs Ann. Chem.*, 1485 (1986).

[5] R. J. Suhadolnik, in Nucleosides as Biological Probes, Wiley-Interscience, New York, 1979, p 158.

[6] N. J. Cusack, B. J. Hildick, D. H. Robinson, P. W. Rugg and G. Shaw, *J. Chem. Soc., Perkin Trans. I*, 1720 (1973).

[7] K. Eger, T. Storz and S. Spätling, *Liebigs Ann. Chem.*, 1049 (1989).

[8] H. J. Roth and K. Eger, *Arch. Pharm.* (Weinheim), **308**, 252 (1975).

[9] E. C. Taylor and R. W. Hendess, *J. Am. Chem. Soc.*, **87**, 1995 (1965).

[10] S. Gabriel and G. Eschenbach, *Ber.*, **30**, 1126 (1897).

[11] E. Hardegger, Methods in Carbohydrate Chemistry, R. L. Whistler and M. L. Wolfram, eds, Academic Press, New York, I, 1962, p 177.

[12a] J. P. Ferris, S. Singh and T. A. Newton, *J. Org. Chem.*, **44**, 173 (1979). [b] L. Andersen, J. Lau and E. B. Pedersen, *Chem. Scripta*, **28**, 307 (1988) and references cited therein.

[13] A. Dornow and A. Müller, *Chem. Ber.*, **93**, 32 (1960).

[14] B. Eistert and H.-K. Witzmann, *Liebigs Ann. Chem.*, **744**, 105 (1971).

[15] R. Fischer and T. Wieland, *Chem. Ber.*, **92**, 1387 (1960).

[16] H. Depuy and B. W. Ponder, *J. Am. Chem. Soc.*, **81**, 4629 (1959).

[17] P. M. Pojer, *Aust. J. Chem.*, **32**, 201 (1979).

[18] S. H. Pines, J. M. Chemerda and M. A. Kozlowski, *J. Org. Chem.*,

31, 3446 (1966).

[19] K. Gewald, *Z. Chem.*, **1**, 349 (1961).

[20] K. Gewald, E. Schinke and H. Böttcher, *Chem. Ber.*, **99**, 94 (1966).

[21] R.-L. Sarantaus-Zimmermann, K. Eger and H.-J. Roth, *Arch. Pharm.* (Weinheim), **314**, 127 (1981).

[22] A. Dornow and E. Neuse, *Arch. Pharm.* (Weinheim), **288**, 177 (1955).

[23] J. Davoll, *J. Chem. Soc.*, 131 (1960).

[24a] H.-D. Winkeler and F. Seela, *Liebigs Ann. Chem.*, 708 (1984) and references cited therein; [b] C. Srivastara and R. K. Robins, *J. Heterocyclic Chem.*, **18**, 1659 (1981).

[25a] N. K. Saxena, B. M. Hagenow, G. Genzlinger, S. R. Turk, J. C. Drach and L. B. Townsend, *J. Med. Chem.*, **31**, 1501 (1988); [b] F. Seela, H.-D. Winkeler, J. Ott, Q.-H. Tran-Thi, D. Hasselmann, D. Franzen and W. Bußmann, *Nucleosides*, **8**, 181 (1981).

[26a] M. P. LaMontagne, D. C. Smith and G.-S. Wu, *J. Heterocyclic Chem.*, **20**, 295 (1983); [b] F. Seela and A. Kehne, *Liebigs Ann. Chem.*, 1940 (1982).

[27] V. Skaric and M. Jokic, *Croat. Chem. Acta.*, **56**, 125 (1983).

[28] M. J. Robins and P. W. Hatfield, *Can. J. Chem.*, **60**, 547 (1982).

[29a] K. H. Schram and L. B. Townsend, *J. Chem. Soc., Perkin Trans. I*, 1253 (1975); [b] F. Seela and H.-D. Winkeler, *Carbohydr. Res.*, **118**, 29 (1983).

[30] M. J. Robins and R. K. Robins, *J. Am. Chem. Soc.*, **87**, 4934 (1965).

[31] P. Nuhn, A. Zschunke, D. Heller and G. Wagner, *Tetrahedron*, **25**, 2139 (1969).

[32] A. Zschunke and P. Nuhn, *Z. Chem.*, **11**, 68 (1971).

[33] K. Kobayashi and W. Pfleiderer, *Chem. Ber.*, **109**, 3194 (1976).

[34] P. S. Ritch and R. I. Glaser, in Development in Cancer Chemotherapy, R. I. Glazer, ed, CRC Press, Boca Raton 1984, p 1.