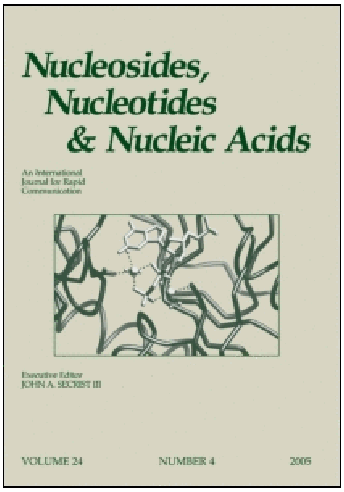
This article was downloaded by:
On: *27 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of 6-Substituted Purine 2'-Azido- and 3'-Azido-Deoxypentopyranoses

Genevieve Carret[a]; Annie Grouiller[a]; Bernard Chabannes[a]; Henri Pacheco[a]
[a] Institut National des Sciences Appliquées de Lyon, Villeurbanne, France

To cite this Article Carret, Genevieve , Grouiller, Annie , Chabannes, Bernard and Pacheco, Henri(1986) 'Synthesis of 6-Substituted Purine 2'-Azido- and 3'-Azido-Deoxypentopyranoses', Nucleosides, Nucleotides and Nucleic Acids, 5: 3, 331 — 342

To link to this Article: DOI: 10.1080/07328318608069982

URL: http://dx.doi.org/10.1080/07328318608069982

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

NUCLEOSIDES & NUCLEOTIDES, 5(3), 331-342 (1986)

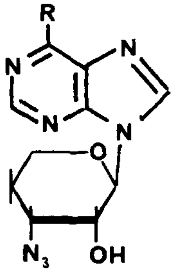
SYNTHESIS OF 6-SUBSTITUTED PURINE 2'-AZIDO- AND 3'-AZIDO-DEOXYPENTOPYRANOSES

Geneviève Carret, Annie Grouiller*, Bernard Chabannes and Henri Pacheco
Institut National des Sciences Appliquées de Lyon, Bât.406
20 Av. A.Einstein, F-69621 Villeurbanne (France)

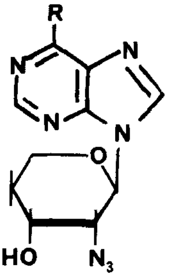
Abstract Various 6-substituted purine 3'-(2'-) azido-3',4'-(2',4'-) dideoxy-β-DL-*erythro*-pentopyranoses (1) (2) have been prepared and compared in terms of a substituent electronegativity parameter. The nucleoside 1a ($R=NH_2$) is a good competitive inhibitor of adenosine deaminase.

Introduction

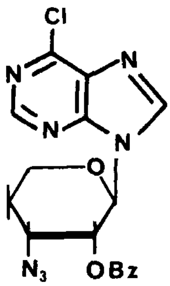
In previous papers we described the synthesis of two pentopyranosyl purines, 9(-3-azido-3,4-dideoxy-α-DL-*threo*-pentopyranosyl)adenine[1] and its *erythro* isomer[2] 1a ($R=NH_2$). In view of the antiviral properties exhibited by the former nucleoside analogue[1] and by various 2'- and 3'-azido-deoxyribofuranosylnucleosides[3-5], we have investigated the synthesis of the corresponding adenine 2'-azido nucleoside 2a ($R=NH_2$). We have also utilized the respective nucleoside precursors 3 and 9 of 1a and 2a for the preparation of various 6-substituted purine derivatives of these both nucleoside analogues[6].



1



2



3

0732-8311/86/0503-0331$3.50/0

Results and Discussion

Synthesis

As in the case of 1a[2], the precursor of 2a was a 6-chloropurine nucleoside, the azidodeoxy-*erythro*-nucleoside 9. The starting compound of its synthesis, methyl 2-azido-3-O-benzoyl-2,4-dideoxy-α or β-DL-*erythro*-pentopyranoside (6), was prepared through the trifluoromethanesulfonylation of the α or β *threo* benzoate 4[7], followed by the azido displacement of the resulting triflate. The triflation occured only with the use of triflic anhydride in the presence of pyridine with ether as solvent, but not in the presence of triethylamine in ether or dichloromethane. The α isomer of the triflate 5 is less stable than the β isomer and has to be kept at -18°C after its dissolution in hexamethylphosphoramide. The azido displacement of the α or β triflate 5 was carried out with lithium azide by heating at 70°C in hexamethylphosphoramide : the only compound formed was the azidodeoxy derivative 6 in agreement with the data of its NMR spectrum. This reaction was accomplished without the pyranose to furanose cycle contraction previously observed in the case of a benzoate displacement[8,9]. There was also no participation of the neighboring 3-benzoyl or 1-methoxy group through an intermediate 2,3-acylonium or 1,2-epoxidium ion, as it occured in the nucleophilic displacement of some furanosyl or pyranosyl sulfonates at C-2[10,11] : neither *threo* isomers of 6 nor an anomeric azido derivative were detected.

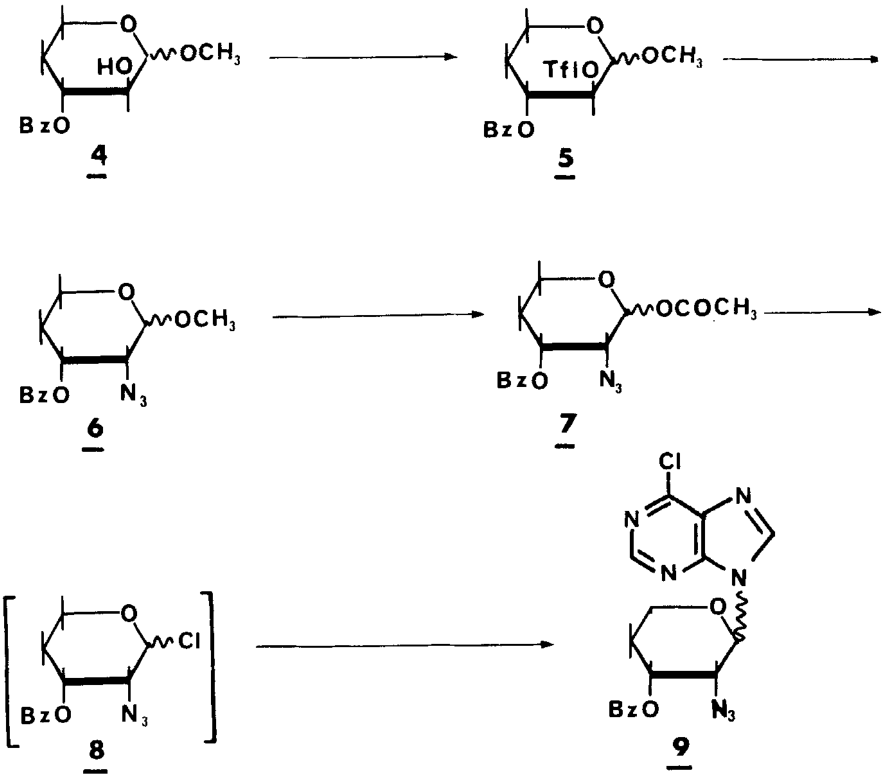
The azidodeoxy derivative 6 was hydrolysed and then acetylated to give the mixture of the α and β anomers 7 in the ratio of 4:1, based on ^{1}H-NMR data. Conversion of 7 into the glycosyl chloride 8, followed by condensation with 6-chloropurine in the presence of mercuric cyanide, according to the method of Yamaoka et al.[12], gave predominantly the β isomer of the 6-chloropurine nucleoside 9, with only 10% of the α isomer. The treatment of 9β with methanolic ammonia afforded the adenine nucleoside 2a.

In order to obtain the various purine nucleosides 1a-g and 2a-c having NH_2, $NHCH_3$, $N(CH_3)_2$ or OCH_2R groups at 6-position, the 6-chloropurine nucleosides 3 and 9 were treated according to the conditions of the Table 1 with the suitable amines or alcoholates in the convenient alcohol. The deprotection of the 3'-hydroxyl accompanied the substitution at C-6.

TABLE 1

Compound No	(mmole)	R, substituent at position 6	Reaction solvent (ml)	Nucleophile	Reaction time h	(temp.)	Yield %	m.p. °C	Rf (AcOEt-EtOH 15:1)	Molecular formula *
1a[2]	(0.53)	NH_2	n.propanol (7)	NH_3 (saturated at 0°C)	72	(R.T.)	90	254-255	0.14	$C_{10}H_{12}N_8O_2$
1b	(0.58)	$NHCH_3$	n.butanol (6)	CH_3NH_2 (3ml)	1	(R.T.)	77	211-212	0.28	$C_{11}H_{14}N_8O_2$
1c	(0.54)	$N(CH_3)_2$	methanol (2)	$(CH_3)_2NH$ (4ml)	1	(R.T.)	95	228	0.46	$C_{12}H_{16}N_8O_2$
1d	(0.72)	Cl	n.propanol (4)	Et_3N (2ml)	72	(R.T.)	75	186-187	0.68	$C_{10}H_{10}ClN_7O_2$
1e	(0.54)	OCH_3	methanol (3)	$NaOCH_3$ (100 mg)	1/2	(60°C)	93	206-207	0.55	$C_{11}H_{13}N_7O_3$
1f	(0.62)	OCH_2CH_3	ethanol (10)	$NaOCH_2CH_3$ (200 mg NaOH)	5	(60°C)	84	226-227	0.60	$C_{12}H_{15}N_7O_3$
1g	(0.88)	$OCH_2CH_2OCH_3$	2-methoxy ethanol (10)	$NaOCH_2CH_2OCH_3$ (100 mg NaOH)	20	(60°C)	84	222-223	0.46	$C_{13}H_{17}N_7O_4$
2a	(0.52)	NH_2	methanol (5)	NH_3 (saturated at 0°C)	96	(R.T.)	81	182-183	0.21	$C_{10}H_{12}N_8O_2$
2b	(0.51)	$NHCH_3$	n.butanol (3)	CH_3NH_2 (3ml)	4	(R.T.)	91	177-178	0.4	$C_{11}H_{14}N_8O_2$
2c	(0.52)	$N(CH_3)_2$	methanol (3)	$(CH_3)_2NH$ (6ml)	96	(R.T.)	98	210-211	0.14	$C_{12}H_{16}N_8O_2$

* Satisfactory microanalyses obtained



(For simplicity, only the D series is depicted in this scheme)

Spectroscopic studies

Ultraviolet absorption properties, as shown in Table 2, supported the N-9 glycosylation and the nature of the substitutions at C-6 : the maximum at higher wavelength of the nucleosides 1a-g and 2a-c was in relative good agreement with the maximum calculated from the literature[13] in function of the 6- electron-donating group, 253 (OCH_3), 260 (NH_2), 266 ($NHCH_3$) and 275 $N(CH_3)_2$.

The NMR assignment of H_2 and H_8 signals were done according to the work of Schweizer et al.[14] and Bullock et al.[15] : the nucleosides were heated in D_2O at 100°C for 10 to 20 min. The intensity of the high field peak decreased because of an exchange of the 8-proton with deuterium. The low field peak which was unaffected was assigned to the 2-proton. Coburn et al.[16] have correlated the proton magnetic resonance chemical shifts of H-8 for 2,6-disubstituted purines with some reactivity parameters such as Brown's electrophilic substituent constant σ_p^+ .

TABLE 2

Compound	R, substituent	UV λ_{max} (ε)	Proton NMR Data ($Me_2SO - d_6$) (δ in ppm, J in Hz)											σ_p
NO	at position 6	(EtOH)	δH-1'	δH-2'	δH-3'	$J_{1'2'}$	$J_{2'3'}$	δH-4'	δH-5'	δH-8	δH-2	$\Delta\delta$ δH-8 - δH-2	δR	
1a	NH_2	260 (12,000)	5.58	4.55	4.32	9.3	3.6	1.90	3.75	8.25	8.10	0.15	7.18	-0.66
1b	$NHCH_3$	260 (16,000)	5.65	4.60	4.35	9.3	3.6	1.88	3.78	8.32	8.25	0.07	7.65 (NH) 4.85 (CH_3)	-0.84
1c	$N(CH_3)_2$	275 (15,000)	5.65	4.50	4.32	9.0	3.6	2.02	3.75	8.30	8.20	0.10	3.45	-0.83
1d	Cl	266 (8,900)	5.70	4.52	4.30	9.1	3.8	1.91	3.75	8.80	8.70	0.10		0.23
1e	OCH_3	250 (15,000)	5.70	4.58	4.32	9.3	4.2	1.88	3.75	8.55	8.50	0.05	4.10	-0.27
1f	OCH_2CH_3	248 (12,000)	5.80	4.70	4.40	9.3		1.90	3.82	8.62	8.52	0.10	4.65 (CH_2) 1.42 (CH_3)	-0.24
1g	$OCH_2CH_2OCH_3$	246 (12,000)	5.75	4.70	4.37	9.0		1.90	3.80	8.62	8.57	0.05	4.70 (CH_2) 3.80 (CH_2) 3.70 (CH_3)	
2a	NH_2	258 (6,600	6.0	5.80	4.20	10.5	4.0	1.83	4.20	8.50	8.23	0.27	7.77	
2b	$NHCH_3$	255 (15,000)	6.0	4.47	4.47	10.4		1.83	3.93	8.53	8.39	0.14	3.07	
2c	$N(CH_3)_2$	274 (16,000	6.03	4.20	4.20	10.0		1.87	4.20	8.53	8.37	0.16	3.53	

In our case a good linear correlation was established as shown in Figures 1 and 2 when δ_{H-2} and δ_{H-8} of the six nucleosides 1a-f were plotted against the 6-substituent parameters σ_p calculated by Daniel and Brown[17] : for δ_{H-2} $r = 0.98$, $n = 6$; for δ_{H-8} $r = 0.99$, $n = 6$. Thus the chemical shifts of H-2 and H-8 are controlled by the electronic effect of the 6-substituent. The unknown value of σ_p for the methoxyethyl group was deduced from this correlation and the p.m.r. data of the nucleoside 1g : $\sigma_p = -0.12$. The weak relative proton chemical shifts ($\Delta\delta = \delta_{H-8} - \delta_{H-2}$) ascertained again the N-9 glycosylation[18].

Biological activity

In view of the very important role played by adenosine deaminase inhibitors in Chemotherapy and Immunosuppression[19], we have examined the susceptibilities to adenosine deaminase (ADA) of all the synthesised nucleosides 1a-g and 2a-c. Calf intestinal mucosa adenosine deaminase (0.8 unit per mg) (EC 3.5.4.4.) was purchased from Sigma Chemical Company. The assay procedure was based upon that of Kaplan[20]; however the deamination and the formation of inosine were not followed spectroscopically, but with HPLC according to a new method involved in our laboratory[21]. Briefly adenosine deaminase (0.005 unit) was incubated in an 1 ml final volume at 37°C for various time with 50 mM potassium phosphate buffer (pH 7.0), 10 to 140 µM adenosine and tested nucleosides in the range concentration of 10^{-5} to 10^{-3} M. The nucleosides were dissolved in 100 µl DMSO. For the blanks, the incubation mixture contains 100 µl DMSO without effector. At the end of incubation, 100 µl of 4N perchloric acid was added followed by 100 µl of 5N potassium acetate and the mixture cooled at 0°C. After centrifugation at 1000 x g, the supernatant was analyzed by HPLC[22]. The column was µ-Bondapak-C18 (Waters). The mobile phase was 0.1 M sodium acetate buffer (pH 3.6) containing 3.5 % ethylalcohol (flow rate 1.5 ml per min). Inosine formed was assayed by comparing the height of its peak with the height of a standard peak run in the same way. The inosine production was linear for at least 30 min at all adenosine and nucleoside concentration used. Only 9(3-azido-3,4-dideoxy-β-DL-*erythro*-pentopyranosyl)adenine 1a was found to be a good competitive inhibitor of the deamination of adenosine, with a $K_i = 45 \times 10^{-5}$ M (K_m for adenosine = 66.7×10^{-6} M). These nucleosides were not substrates for adenosine deaminase. From the studies of other nucleosides, it was precedently noticed that no pyranosyl nucleoside has ever served as a substrate[23].

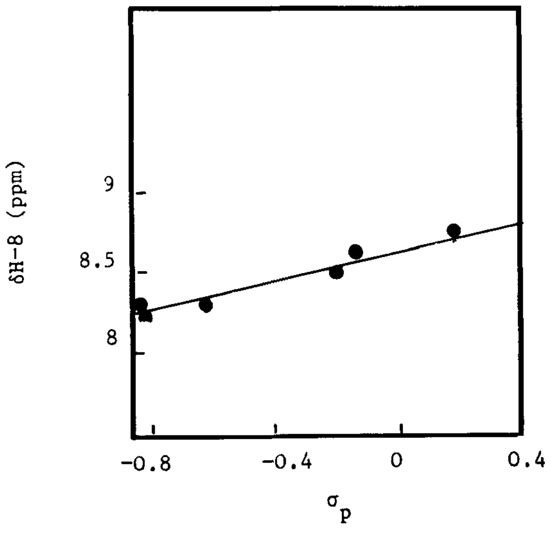


FIG. 1

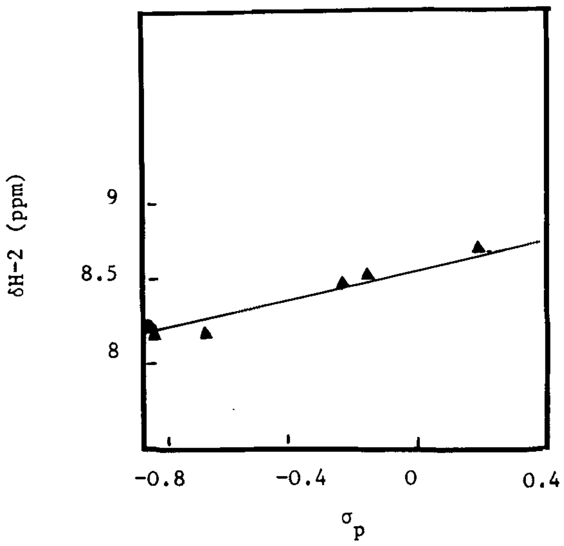


FIG. 2

Plots of the Chemical shifts δH-8 (Fig. 1) and δH-2 (Fig. 2) *vs*. the 6-substituent parameters σ_p:

Experimental

General Methods. Melting points were determined with a Kofler melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded with a Brucker WP-80 spectrometer and are reported relative to the tetramethylsilane signal. IR spectra were recorded with a Beckman Acculab-4 spectrophotometer and UV spectra with a Beckman DBG spectrophotometer. Column chromatography was performed on Silica Gel 60 F_{254} (Merck), and TLC on Silica Gel 60 F_{254} aluminum sheets (Merck); substances were made visible by spraying with the phosphomolybdic acid reagent and heating at 120°C. Elemental analyses were performed by the Service Central d'Analyse du CNRS.

Methyl 3-O-benzoyl-4-deoxy-2-O-trifluoromethanesulfonyl-α or β-DL-*threo*-pentopyranosides (5)

To a magnetically stirred suspension of 3Å molecular sieve (10 g) in anhydrous ether (200 ml) and dry pyridine (4.5 ml) was rapidly added at 0°C trifluoromethanesulfonic anhydride (20g, 70.9 mmole), then a solution of 4α or 4β (5g, 19.8 mmole)[7] in anhydrous ether (100 ml). The reaction mixture was kept for 3h at room temperature, then filtered. The filter cake was washed with ether and the combined filtrates with cold 5% sodium hydrogencarbonate (3x100 ml) and then water (2x100 ml). The organic layer was dried (sodium sulfate) and evaporated under reduced pressure (130 Pa, 15°C). The crude crystalline product formed 5 was immediately used for the next step (for analytical purposes, a sample was purified by silica gel column chromatography with 1:2 (v/v) ether-pentane as eluent)

5α (5.7g, 75%) : mp 102-103°C. TLC (ether-pentane, 1:10) R_f 0.41 IR(KBr) : ν_{max} 1740, 1610, 1420, 1230 and 1080 cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 7.37 (m, 5H, Ar), 5.23 (m, 1H, H-3), 4.7 (dd, 1H, $J_{2,3}$ 9Hz, $J_{2,4e}$ 5.33Hz, $J_{2,4a}$ 10.4Hz, H-2), 4.37 (d, 1H, $J_{1,2}$ 6.83Hz, H-1), 4.03 (m, 1H, $J_{5e,5a}$ 12.3Hz, $J_{5e,4a}$ 5.17Hz, $J_{5e,4e}$ 2.66Hz, H-5e), 3.53 (s and m, 3H and 1H, OCH_3 and H-5a), 2.3 (m, 1H, $J_{4e,3a}$ 5.33Hz, $J_{4e,4a}$ 13Hz, $J_{4e,5a} = J_{4e,5e}$ 2.66Hz, H-4e), 1.7 (m, 1H, $J_{4a,3a}$ 10.5Hz, $J_{4a,5a}$ 9.3Hz, $J_{4a,5e}$ 5.17Hz, H-4a).

Anal. Calcd for $C_{14}H_{15}F_3O_7S$: C,43.75; H,3.9; F,14.84; S,8.33.
Found : C,43.68; H,3.93; F,15.0; S,8.13.

5β (7.5g, 98%) : mp 99-100°C. TLC (ether-pentane, 1/10) R_f 0.59 IR(KBr) : ν_{max} 1740, 1610, 1420, 1220-1210 and 1060 cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 7.68 (m, 5H, Ar), 5.56 (m, 1H, H-3), 5.1 (m, 2H, $J_{1,2}$ 3.5Hz,

$J_{2,3}$ 10.6Hz, H-1 and H-2), 3.53 (m, 2H, H-5a and H-5e), 3.47 (s, 3H, OCH_3), 2.03 (m, 2H, H-4a and H-4e).

Anal. Calcd for $C_{14}H_{15}F_3O_7S$: C,43.75; H,3.9; F,14.84; S,8.33.
Found : C,43.99; H,3.90; F,15.08; S,8.30.

Methyl 2-azido-3-O-benzoyl-2,4-dideoxy-α or β-DL-*erythro*-pentopyranoside 6

To a stirred solution of 5α or 5β (6g, 15.6 mmole) in freshly distilled N,N',N" hexamethylphosphoric triamide (120 ml) were added 3Å molecular sieve (3g) and lithium azide (3g, 61 mmole). The mixture was heated for 1.5h at 70°C, while monitoring the reaction by IR (disappearance of the sulfonyl band at 1420 cm^{-1} and appearance of the azido band at 2120 cm^{-1}). After the mixture had been cooled, the solution was taken up with water, then extracted with ether. The organic layer was dried (sodium sulfate) and evaporated. The crude product was chromatographed on a silica gel column with 1:3 (v/v) ether-pentane as eluent to give 6 as an oil which crystallizes in the case of the β isomer.

6α (2.43g, 88%) : TLC (ether-pentane, 1:2.5) R_f 0.41. IR(KBr) : ν_{max} 2120, 1720, 1610 and 1270 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.77 (m, 5H, Ar), 5.33 (ddd, 1H, $J_{3,4a}$ 8Hz, $J_{3,4e}$ 3.33Hz, H-3), 4.6 (d, 1H, $J_{1,2}$ 2.17Hz, H-1), 4.06 (ddd, 1H, $J_{5e,5a}$ 12Hz, $J_{5e,4e}$ 4.66Hz, H-5e), 3.50 (m, 2H, $J_{2,3}$ 4.66Hz, H-2, H-5a), 3.57 (s, 3H, OCH_3), 2.0 (m, 2H, H-4a, H-4e).

Anal. Calcd for $C_{13}H_{15}N_3O_4$: C,56.32; H,5.41; N,15.16; O,23.10.
Found : C,56.60; H,5.32; N,14.95; O,23.08.

6β (2.57g, 93%) : mp 70-71°C. TLC (ether-pentane, 1:2.5) R_f 0.59. IR(KBr) : ν_{max} 2120, 1720 and 1270 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.8 (m, 5H, Ar), 5.57 (ddd, 1H, $J_{3,4e}$ 3.6Hz, $J_{3,4a}$ 8.9Hz, H-3), 4.73 (d, 1H, $J_{1,2}$ 3.33Hz, H-1), 3.83 (m, 3H, $J_{2,3}$ 5.3Hz, H-2, H-5a, H-5e), 3.47 (s, 3H, OCH_3), 2.0 (m, 2H, H-4a, H-4e).

Anal. Calcd for $C_{13}H_{15}N_3O_4$: C,56.32; H,5.41; N,15.16; O,23.10.
Found : C,56.40; H,5.29; N,15.02; O,23.19.

1-O-Acetyl-2-azido-3-O-benzoyl-2,4-dideoxy-α- and -β-DL-*erythro*-pentopyranose 7.

Compound 6α or 6β (4g, 14.4 mmole) was hydrolyzed by heating its solution in glacial acetic acid (30 ml) with concentrated hydrochloric acid (5.5 ml) and 10Å molecular sieve powder (1g) for 7h at 50°C. The solution was made neutral with sodium hydrogencarbonate (5.5g) and evaporated to dryness (50°C) under reduced pressure. The residue was suspended in chloroform (20 ml) and pyridine (20 ml). After addition of acetic anhydride (17 ml), the suspension was stirred for 6h at 35°C and evaporated in vacuo. The residue was diluted with ice-hydrochloric acid and extracted with chloroform. The organic layer was washed successively with 5% aqueous sodium hydrogencarbonate and water. After being dried (sodium sulfate), the chloroform extract was evaporated. The residual oil was chromatographed on a silica gel column with 1:4 (v/v) ether-pentane as eluent to afford both α and β anomers of 7 in a 4:1 ratio (3.5g, 80%).

7α : oil. TLC (ether-pentane 1:2.5) R_f 0.5. IR(KBr) : ν_{max} 2120, 1750, 1720, 1600 and 1580 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.83 (m, 5H, Ar), 6.03 (d, 1H, $J_{1,2}$ 2.67Hz, H-1), 5.47 (ddd, 1H, $J_{3,4a}$ 6.67Hz, $J_{3,4e}$ or $J_{3,2e}$ 3.34 or 4.67Hz, H-3), 4.03 (m, 2H, H-5a, H-5e), 3.80 (dd, 1H, H-2), 2.27 (s, 3H, OAc), 2.13 (m, 2H, H-4a, H-4e).

7β : oil. TLC (ether-pentane 1:2.5) R_f 0.4. ^1H NMR ($CDCl_3$) : δ 7.80 (m, 5H, Ar), 6.10 (d, 1H, $J_{1,2}$ 3.73Hz, H-1), 5.60 (ddd, 1H, $J_{3,4a}$ 8.33Hz, $J_{3,4e}$ or $J_{3,2e}$ 3.33 or 4.83 Hz, H-3), 3.9 (m, 3H, H-2, H-5a, H-5e), 2.1 (s + m, 5H, OAc, H-4a, H-4e).

Anal. Calcd for $C_{14}H_{15}N_3O_5$ (mixture) : C,55.08; H,4.92; N,13.77; O,26.23. Found : C,55.09; H,4.89; N,13.68; O,26.25.

9-(2-Azido-3-O-benzoyl-2,4-dideoxy-α- and β-DL-*erythro*-pentopyranosyl)-6-chloropurine 9.

To a solution of 7 (1.35g, 4.43 mmole) in anhydrous ether (20 ml) were added molecular sieve 3Å (3g) and acetyl chloride (1.5 ml, 21 mmole). Through this solution, cooled to 0°C, was bubbled dry hydrogen chloride until the gas escaped from the drying tube. The mixture was then kept for 6h at room temperature. Evaporation of the mixture to dryness gave a pale-yellow foam, which was immediately dissolved in dry nitromethane (25 ml). To this solution were added molecular sieve 3Å (1.5g), 6-chloropurine (1.35g, 8.73 mmole) and mercuric cyanide (1.35g, 5.34 mmole), and the mixture was heated under reflux for 4h. The reaction mixture was filtered hot, and the filter cake was washed with hot nitromethane. After evaporation of the combined filtrates, the residue was extracted with chloroform, which was washed consecutively with 30% potassium iodide in half-saturated sodium chloride (80 ml) and saturated sodium chloride (2x30 ml). Evaporation of the dried organic layer gave 9 as an oily mixture of the α and β anomers that was chromatographed on a column of silicic acid using ether-pentane (2:1) giving a clear separation of the two anomeric products. Elution of the first minor isomer gave 131 mg (7.4%) of 9α; continued elution with the same solvent gave 1.32g

(74.6%) of 9β, mp 169-170°C. TLC (ether-pentane, 2:1) R_f 0.36. IR(KBr) : ν_{max} 2120, 1720, 1600 and 1560 cm^{-1}. UV(EtOH) : λ_{max} 232 (ε 21,000) and 262 (ε 12,200) nm. ^1H NMR (Me_2SO-d_6) : δ 9.17 and 9.0 (2s, 2H, H-2 and H-8), 8.0 (m, 5H, Ar), 6.23 (d, 1H, $J_{1',2'}$ 10.5Hz, H-1'), 6.0 (m, 1H, $J_{3',4'e}$ 2.5Hz, $J_{3',4'a}$ 3.3Hz, H-3'), 5.17 (dd, 1H, $J_{2',3'}$ 3Hz, H-2'), 3.97 (m, 2H, H-5'e, H-5'a), 2.17 (m, 2H, H-4'a, H-4'e).

Anal. Calcd for $C_{17}H_{14}ClN_7O_3$: C,51.06; H,3.50; Cl, 8.88; N,24.53. Found : C,50.84; H,3.37; Cl, 9.08; N,24.35.

6-Substituted purine nucleosides 1a-g and 2a-c.

The general procedure was to react 3[2] or 9 with the suitable nucleophile in an alcoholic solution according to the conditions described in the Table 1. The reaction mixture was evaporated in vacuo (in the case of 1e-g, the solution was neutralized with 0.5N chlorhydric acid before the evaporation). The product was then purified by chromatography on a column of silicic acid using elution with ethyl acetate - ethanol.

Acknowledgments

This investigation was supported in part by the Centre National de la Recherche Scientifique (UA 04 495) and in part by the Institut National de la Santé et de la Recherche Médicale (U.205).

References

1. D. Bouchu, M. Abou-Assali, A. Grouiller, G. Carret and H. Pacheco, Eur. J. Med. Chem., 16 (1), 43 (1981).
2. G. Carret, A. Grouiller and H. Pacheco, Carbohydr. Res., 111, 59 (1982).
3. E. De Clercq, J. Balzarini, J. Descamps and F. Eckstein, Biochem. Pharmacol., 29, 1849 (1980).
4. M. Ikehara and Y. Takatsuka, Chem. Pharm. Bull., 26 (3), 985 (1978).
5. L. Colla, P. Herdewijn, E. De Clercq, J. Balzarini and H. Vanderhaeghe, Eur. J. Med. Chem., 20 (4), 295 (1985).
6. This work is a part of the thesis of G. Carret (Dissertation N°90, Université Claude Bernard - Lyon I, 1984).
7. D. Picq, D. Anker and H. Pacheco, Tetrahedron Lett. 22 (45), 4517 (1981).
8. A. Grouiller, H. Bazin and C. Gagnieu, Tetrahedron Lett., 23 (25), 2559 (1982).

9. A. Grouiller, accepted in Can. J. Chem.

10. K.J. Ryan, H. Arzoumanian, E.M. Acton and L. Goodman, J. Am. Chem. Soc., 86, 2497 (1964).

11 K.J. Ryan, E.M. Acton and L. Goodman, J. Org. Chem., 36, 2646 (1971).

12. N. Yamaoka, K. Aso and K. Matsuda, J. Org. Chem., 30, 149 (1965).

13. A. Pullman, Bull. Soc. Chim. France, 641 (1958).

14. M.P. Schweizer, S.I. Chan, G.K. Helmcamp and P.O.P. Ts'O. J. Amer. Chem. Soc., 86, 696 (1964).

15. F.J. Bullock and O. Jardetzky, J. Org. Chem. 29, 1988 (1964).

16. W.C. Coburn, M.C. Thorpe, J.A. Montgomery, and K. Hewson, J. Org. Chem., 30, 1114 (1965).

17. Paramètres électroniques. Busch; Ecole européenne d'été QSAR (1976).

18. L.B. Townsend in W.W. Zorbach and R.S. Tipson, Eds., Synthetic Procedures in Nucleic Acid Chemistry, Vol.2, Interscience, New-York, 318 (1973).

19. R.I. Glazer, Cancer Chemother. Pharmacol., 4, 227 (1980).

20. N.O. Kaplan, Methods Enzymol., 2, 473 (1955).

21. B. Chabannes, submitted to J. of Enzyme inhibition.

22. B. Chabannes; J.N. Bidard, N. Sarda and L. Cronenberger, J. Chromatogr., 170, 430 (1979).

23. A.J. Grant and L.M. Lerner, Biochimica and Biophysica Acta, 525, 472 (1978).

Received December 20, 1985.