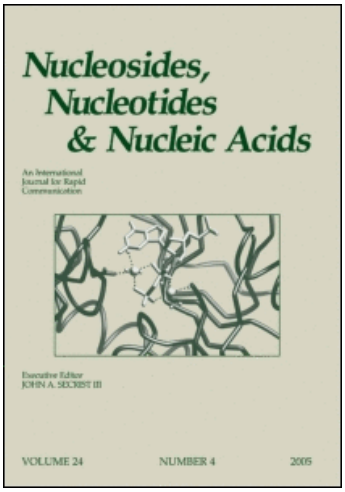


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# Application of the Transpuriation Reaction to Synthesis of Acyclic Guanosine Analogues

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# APPLICATION OF THE TRANSPURINATION REACTION TO SYNTHESIS OF ACYCLIC GUANOSINE ANALOGUES

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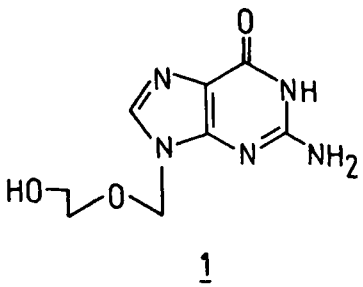
ABSTRACT: A novel transpurination reaction of tetraacetylguanosine was successfully applied for the preparation of 9-(2-hydroxyethoxymethyl)- and 9-(1,3-dihydroxy-2-propoxymethyl)guanines (compounds 1 and 2, respectively). Yield of the desired 9-isomers was significantly increased by application of the thermal 7⇌9 transglycosylation.



Chemical synthesis of nucleoside analogues modified in the sugar portion has recently received much attention due to the discovery of acyclonucleosides with potent antiviral activity[1]. In particular, 9-(2-hydroxyethoxymethyl)guanine (1: acycloguanosine, acyclovir or Zovirax) and 9-(1,3-dihydroxy-2-propoxymethyl)guanine (2: DHPG, ganciclovir, 2'-NDG or BIOLF-62) have been shown to be the most effective antiviral agents among the guanosine analogues.

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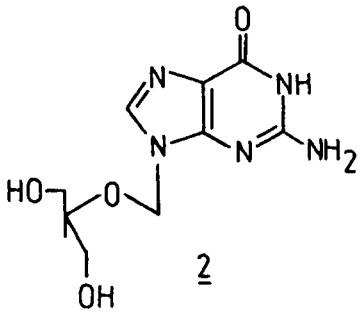


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In search for a simple and general approach to synthesis of nucleoside analogues with a modified sugar portion we have recently proposed a transpurination method[2].

The transpurination may be consider as a counterpart reaction of the better known transglycosylation, originally developed by Miyaki et al.[3] as a method of nucleoside synthesis. In that approach, conversion

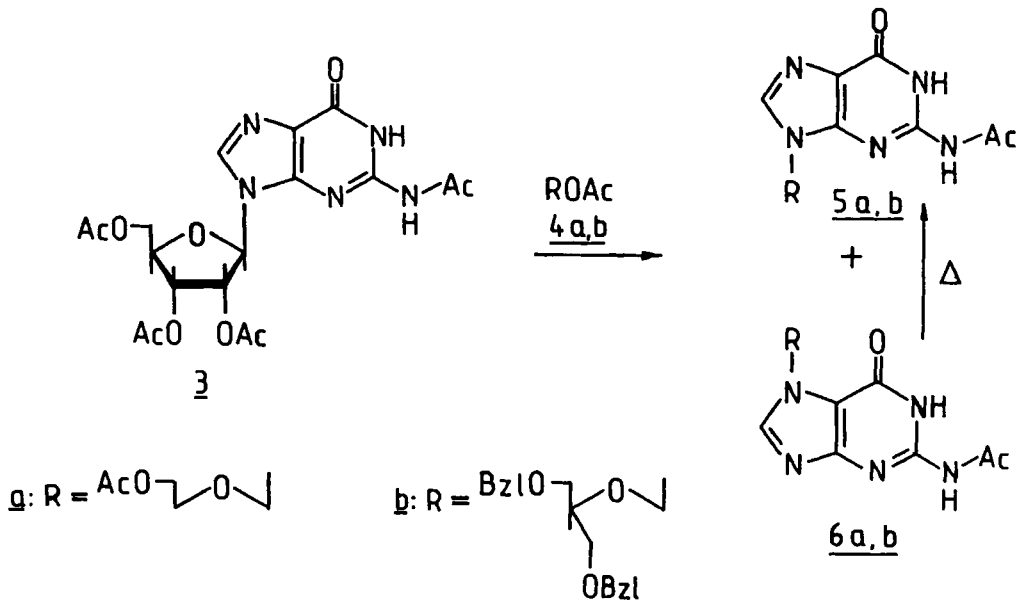
of pyrimidine to purine ribonucleosides was achieved in moderate yield by heating of fully acylated uridine or cytidine with an excess of purine bases as glycosyl acceptors and in the presence of mercuric bromide. More recently, Azuma and Isono[4] improved the transglycosylation method using silylated purine bases and trimethylsilyl trifuoromethanesulfonate as a catalyst. Other examples of transglycosylation from pyrimidines to purines were given by Imazawa and Eckstein[5].

In all the cases presented above a fully protected ribonucleoside served as the glycosyl donor. For synthesis of acyclonucleosides we applied a counterpart approach - use of a relatively accessible ribonucleoside as a donor of the nucleobase in reaction with another fully protected sugar or its acyclic analogue[2]. The reaction, named "transpurination"[5a], was originally noticed by Lichtenthaler and Kitahara[6], who observed migration of hypoxanthine from ribose to glucose when 2',3'-O-isopropylideneinosine and 1-α- bromo-2,3,4,6-tetra-O-acetylglucose were heated in the presence of mercuric cyanide. That interesting reaction, however, has not found any synthetic application so far.

In our synthesis of acyclovir (1), the readily available N-2,2' -O,3' -O,5' -O-tetraacetylguanosine (3)[7] and (2-acetoxyethyl)acetoxymethyl ether (4a)[8] were refluxed in dry chlorobenzene, in the presence of catalytic amount of p-toluenesulfonic acid. After 1 h the transpurination reaction resulted in formation of a 9- and 7-isomeric mixture. Chromatographic separation and crystallization allowed to obtain the diacetyl derivative of acyclovir (5a) in 47% yield in the respect to tetraacetylguanosine (3), and the corresponding 7-isomer (6a) in 39%. The reaction may be performed also without solvent. This approach turned out to be particularly advantageous for preparation of DHPG. Fusion of 3 and 2-(acetoxymethoxy)-1,3-dibenzyloxypropane (4b)[9] at 160°C for 10 min afforded the fully protected derivative of DHPG (5b) in 41% and the respective 7-isomer (6b) in 34%.

In this way the transpurination approach appeared to be a very simple and inexpensive synthetic method for preparation of acylic analogues of guanosine, i.e. acyclovir (1) and DHPG (2), superior in these respects to any laboratory procedure published so far[9-14].

In the case of acycloguanosines the 7- and 9-isomers may be easily separated by crystallization[9] or by a simplified chromatographic method due to a bigger difference in their $R_F$ values comparing to that of 7-

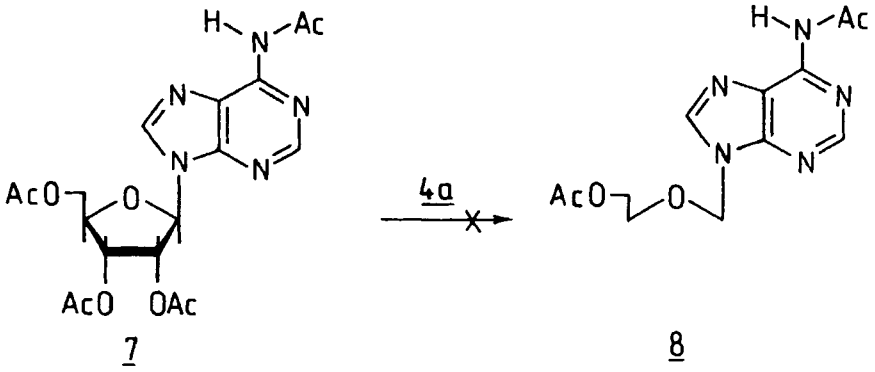



and 9-ribosides. Moreover, the 7-isomers can be converted to the biologically active 9-isomers in the thermal 7⇌9 transglycosylation reaction reported recently[15,16].

Thus, heating of the 7-isomer 6a without solvent and in the absence of catalysts at 230° for 5 min resulted in the mixture of 7-and 9-isomers (6a and 5a, respectively), with the isomeric ratio 7/9 being 45:55, as determined by the proton NMR[16]. In the similar manner, the 7-isomer 6b was transformed to the protected derivative of DHPG (5b) in 48% yield (ratio 7/9 was 48:52). In both cases a prolonged reaction time did not change the isomer distribution, but resulted in small amounts of N-2--acetylguanine.

The fact, that the reversible 7⇌9 transglycosylation proceeded easily in the absence of catalysts, prompted us to repeat the transpurination experiment without p-toluenesulfonic acid. Interestingly, fusion of 3 and 4a without any catalyst added (200°, 10 min) afforded small amounts of the 9- and 7-isomers of diacetyl acyclovir (5a and 6a), respectively). It may be an indication, that both discussed reactions, i.e. transpurination and 7⇌9 transglycosylation, are closely related. Moreover, susceptibilities to the transpurination and to the 7⇌9 reversible transglycosylation are also similar in the tested series of

purine derivatives. The protected derivatives of guanine readily underwent the 7⇌9 glycosyl migration reaction [15] and were good substrates in the transpurination procedure. On the other hand, tetraacetyladenosine (7) did not undergo the termal interconversion to the 7-isomer at 200°C[15], and was unreactive in an attempted transpurination reaction. Heating of 7 and 4a under conditions suitable for synthesis of acyclovir did not afford the acylic compound 8.




7 8

In either transpurination or thermal 7⇌9 transglycosylation reactions of protected guanine derivatives, formation of 7,9-disubstituted intermediates was not observed, as judged by the NMR and TLC. Compounds of this type, i.e. 7,9-diglycosyl hypoxanthines, were isolated in the case of related reactions performed under considerably milder conditions[6,17]. Nevertheless, it is very likely that both transpurination and 7⇌9 transglycosylation may proceed via initial formation of a 7,9-disubstituted intermediate, which is extremely unstable under the drastic conditions applied. Its decomposition may give rise to the observed mixture of 7- and 9-isomers.

## EXPERIMENTAL

Melting points were determined on a micromelting point apparatus in open capillaries and are uncorrected. The ultraviolet spectra were measured in water on a Zeiss Specord UV-Vis and on a Zeiss VSU-2P spectrophotometer. The $^1$H NMR spectra were recorded on a JEOL FX 90Q FT NMR spectrometer in $d_6$-dimethylsulfoxide with $Me_4Si$ as internal standard

and are reported in ppm on the $\delta$ scale. Thin-layer chromatography was conducted on Merck precoated silica gel $F_{254}$ Type 60 plates and $R_F$ values are given for chloroform-methanol (9:1, v/v). For a preparative short column chromatography Merck TLC gel H Type 60 was used. Elemental analyses were performed on a Perkin-Elmer 240 Elemental Analyzer and a Hewlett-Packard 185 CHN Analyzer.

N-2,2'-O,3'-O,5'-O-Tetraacetylguanosine (3) was prepared as described by Reese and Saffhill[7], and then precipitated from chloroform to ethyl ether to get a white powder. The compounds 4a and 4b were obtained according to known procedures (Ref. 8 and 9, respectively). For further structure confirmation the products 5a and 5b were deprotected and found to be identical with authentic samples of acyclovir and DHPG, respectively.



9-(2-Acetoxyethoxymethyl)-N-2-acetylguanine (5a). Tetraacetylguanosine (3: 1.0 g, 2.215 mmol), (2-acetoxyethyl)acetoxymethyl ether (4a: 1.17 g, 6.65 mmol) and p-toluenesulfonic acid monohydrate (84 mg, 0.443 mmol) were refluxed in dry chlorobenzene (10 mL) for 1 h. The resultant mixture was evaporated to an oil, which was dissolved in chloroform and applied on a silica gel short column (3.8 x 9 cm). Elution was performed with a chloroform-methanol gradient (from 95:5 to 9:1, respectively), and 20-mL fractions were collected. Fractions 22-29 contained chromatographically pure 7-isomer (6a), 269 mg (39%) after evaporation and crystallization from ethanol, mp. 187°C; $R_F$ 0.39; UV $\lambda_{max}$ 221 nm ($\varepsilon$ 20,300), 264 (14,100) and 280 (sh; 10,400), $^1$H NMR 1.95 (s,3,$OCH_3CO$), 2.17 (s,3,$NCH_3CO$), 3.71 and 4.08 (2m,4,$CH_2CH_2$), 5.69 (s,2,$NCH_2O$), 8.36 (s.1,8-H).

Anal. Calcd. for $C_{12}H_{15}N_5O_5$ (309.28): C, 46.60; H, 4.89; N, 22.64 Found: C, 46.73; H, 4.78; N, 22.40.

Upon evaporation of fractions 33-47 homogenous by TLC 9-isomer (5a) was obtained as a crystallizing solid. Recrystallization from methanol afforded 324 mg (47%) of the diacetyl derivative of acyclovir (5a), mp. 204°C. $R_F$ 0.22 UV $\lambda_{max}$ 259 mm ($\varepsilon$ 16,600) and 280 (sh, 11,900); $^1$H NMR 1.95 (s,3,$OCH_3CO$), 2.19 (s,3,$NCH_3CO$), 3.71 and 4.06 (2m,4,$CH_2CH_2$), 5.48 (s,2,$NCH_2O$), 8.14 (s,1,8-H).

Anal. Calcd. for $C_{12}H_{15}N_5O_5$ (309.28); C, 46.60; H, 4.89; N, 22.64. Found: C, 46.68; H, 4.90; N, 22.15.

Conversion of 6a into 5a. The 7-isomer 6a (1.0 g, 3.233 mmol) prepared according to the above procedure, was heated in an open flask on an oil bath at 230° for 5 min. The resultant yellow oil was dissolved in chloroform-methanol (95:5) and a small sample was taken for the $^1H$ NMR, what revealed the isomeric ratio 7/9 being as 45:55. The rest of solution was applied on a silica gel column. Chromatographic separation performed as described above gave 403 mg (40%) of the unreacted 6a and 509 mg (51%) of 5a. The products were identical in all respects with those obtained in the transpurination method.

9-(1,3-Dibenzyloxy -2- propoxymethyl)-N-2-acetylguanine (5b). Tetra-acetylguanosine (3; 2.5 g, 5.538 mmol), the dibenzyl derivative 4b (6.0 g, 17.42 mmol) and p-toluenesulfonic acid monohydrate (84 mg, 0.443 mmol) were heated on an oil bath at 160° for 10 min. The obtained oil was dissolved in chloroform-methanol (98:2, 15 mL) and applied on a silica gel column (6,5 x 13 cm). Products were eluted with a chloroform--methanol gradient (from 98:2 to 95:5), 20-mL fractions. Evaporation of fractions 73-86 afforded the 7 isomer 6b as a homogenous by TLC solid foam. Yield 895 mg (34%). An analytical sample was crystallized from ethyl acetate[9], mp 133°C; $R_F$ 0.71; UV $\lambda_{max}$ 222 nm (sh; ε 20,000), 264 (14,100) and 280 (sh; 10,500); $^1H$ NMR 2.18 (s,3,$CH_3CO$), 3.46 (m,4, 2x$CH_2$), 4.13 (m,1,CH), 4.41 (s,4, 2x$CH_2Ph$), 5.78 (s,2,$NCH_2O$), 7.24-7.35 (m,10,2x$C_6H_5$), 8.36 (s,1,8-H).

Anal. Calcd. for $C_{25}H_{27}N_5O_5$ (477.52): C, 62.88; H, 5.70; N, 14.67. Found: C, 62.80; H, 5.90; N, 14.65.

Fractions 89-105 contained the desired 9-isomer (5b) in form of a yellow oil after evaporation. The product was crystallized from toluene what gave 1.093 g (41%) of white, crystalline material, mp 147°C; $R_F$ 0.60; UV $\lambda_{max}$ 258 nm ( ε 16,700) and 280 (sh; 11,800) $^1H$ NMR: 2.17 (s,3,$CH_3CO$), 3.41 (m,4,2x$CH_2$), 4.02 (m,1,CH), 4.40 (s,4,2x$CH_2Ph$), 5.57 (s,2, $NCH_2O$), 7.19-7.33 (m,10,2x$C_6H_5$), 8.12 (s,1,8-H).

Anal. Calcd. for $C_{25}H_{27}N_5O_5$ (477.52): C, 62.88; H, 5.70; N, 14.67. Found: C, 62,61; H, 5.59; N, 14,42.

Conversion of 6b into 5b. The reaction was performed as for the 7⇌9 transglycosylation of acyclovir (from 6a to 5a), using 800 mg (1.675 mmol) of 6b. Ratio of 7/9 was 48:52, as determined by the $^1H$ NMR.

Chromatographic separation and crystallization as described above afforded 328 mg (41%) of 6b and 380 mg (48%) of 5b, identical with those

obtained in the transpurination method or prepared according to Martin et al.[9].

Transpurination of 3 in the absence of catalyst. Tetraacetylguanosine (3; 45.1 mg, 0.1 mmol) and 4a (53 mg, 0,3 mmol) were heated on an oil bath at 200° for 10 min. The resultant brown oil was dissolved in chloroform and controlled by TLC, what showed small amounts (ca 15% each) of 5a and 6a along with prevailing amounts of tetraacetylguanosine (3) and its 7-isomer.

Attempted synthesis of 9-(2-acetoxyethoxymethyl)-N-6-acetyladenine (8). Tetraacetyladenosine (7) (200 mg, 0.459 mmol), the diester 4a (243 mg, 1,38 mmol) and p-toluenesulfonic acid monohydrate (4.4 mg, 0,023 mmol) were refluxed in dry chlorobenzene (4 mL) for 1 h. The obtained reaction mixture was evaporated to an oil. The oil was dissolved in chloroform and analyzed by TLC, that showed a prevailing amount of the unreacted 7 ($R_F$ 0.70) and an unstable minor product of $R_F$ 0.59, which decomposed during an attempted chromatographic separation on silica gel in a chloroform-ethanol gradient.

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