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A NOVEL TYPE OF ANHYDRONUCLEOSIDES TO MODEL SYN-CONFORMERS OF NATURAL NUCLEOSIDES

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Abstract: Convenient general method for the synthesis of a new type of anhydronucleosides with syn-orientation of nucleic bases has been developed.

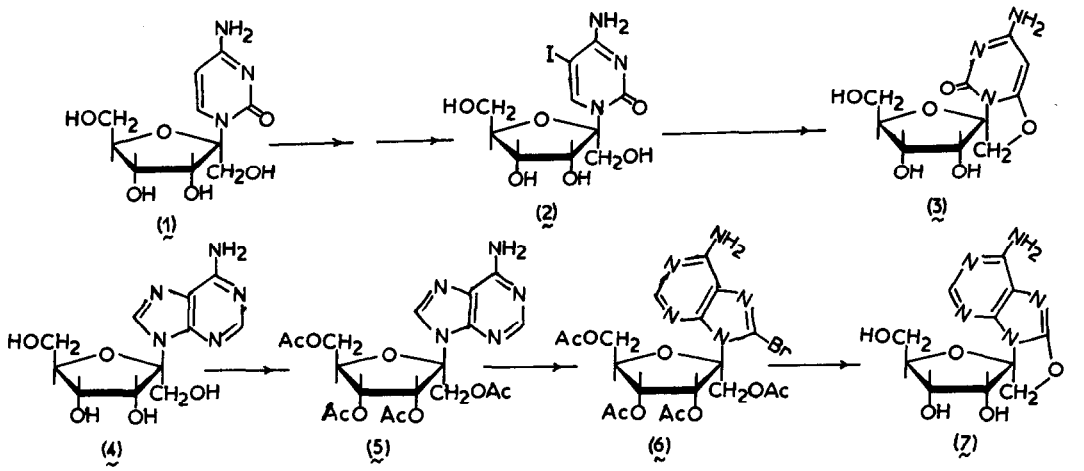
At present, the chemistry of anhydronucleosides both of purine and pyrimidine types has been studied fairly well[1,2]. However, the main progress is achieved in the field of anti-like anhydronucleosides. Although syn-like cyclonucleosides are first representatives of this type compounds[3a] and their synthesis is very common[3a,b], further synthetic and biochemical possibilities of these derivatives are rather limited because of the absence of the necessary hydroxy groups and difference from the natural nucleosides by the ionic and tautomeric forms.

The present paper deals with the synthesis of syn-like anhydronucleosides maintaining the ionic and tautomeric properties as well as all functional groups of parent nucleosides.

An appropriate route for preparation of these substances is cyclization of nucleosides modified at the C(1') atom of the carbohydrate moiety, e.g. 2-β-D-psicofuranosides. This approach has been realized in the case of 6,1'-anhydro-6-hydroxy-1-(2-β-D-psicofuranosyl)cytosine (3) and 8,1'-anhydro-8-hydroxy-9-(2-β-D-psicofuranosyl)adenine (7) synthesis.

Starting compounds, 1-(2-β-D-psicofuranosyl)cytosine (1) and

9-(2-β-D-psicofuranosyl)adenine (psicofuranine or angustmycine C) (4), have been prepared as described earlier[4,5].



Heating (1) with solution of mercury (II) acetate followed by iodo-demercuration of the intermediate affords 5-iodo-1-(2-β-D-psicofurano-syl)cytosine (2) in 75% yield[6], m.p. 161-162° (from H_2O); UV, λ_{max},nm (ε): pH 1 308 (9,320), pH 7 292 (5,960), pH 13 293 (5,990); NMR (^2H_2O), ppm: H(6) 8.43s, H(3') 4.76d ($J_{3',4'}$ 4.5 Hz), H(1'a) 4.24d ($J_{1'a,1'b}$ 12 Hz), H(4') and H(5') 4.3-4.1m, H(1'b) 3.93d, H(6'a) 3.88dd ($J_{5',6'a}$ 3 Hz, $J_{6'a,6'b}$ 12.5 Hz), H(6'b) 3.66dd ($J_{5',6'b}$ 4.5 Hz).

The substituted nucleoside (2) is converted to the anhydronucleoside (3) by treatment with potassium tert-butoxide in anhydrous DMSO at 60°. The yield is 60%, m.p. 256-257° (from H_2O); mass spectrum, m/e 271 (M^+); UV, λ_{max}, nm (ε): pH 1 266 (23,100), pH 7 261 (16,900), pH 13 262 (13,300); CD, λ_{extr}, nm (Δε): pH 7 268 (+1.29); NMR (^2H_2O), ppm: H(5) 5.43s, H(3') 5.25d ($J_{3',4'}$ 5 Hz), H(1'a) 5.02d ($J_{1'a,1'b}$ 10.5 Hz), H(1'b) 4.54d, H(4') 4.38dd ($J_{4',5'}$ 3 Hz), H(5') ~4.07m, H(6'a) and H(6'b) ~3.75m.

Treatment of (4) with acetic anhydride in pyridine at room temperature affords acetylated compound (5) in 93% yield, m.p. 81.5-82.5° (from etha-nol); UV, λ_{max}^{EtOH}, nm (ε): 260 (15,500); NMR (C^2HCl_3), ppm: H(8) 8.31s, H(2) 8.12s, H(3') 6.63d ($J_{3',4'}$ 5 Hz), NH_2 5.99s, H(4') 5.39dd ($J_{4',5'}$ 6.5 Hz), H(1'a) 4.86dd ($J_{1'a,1'b}$ 12 Hz), H(1'b) 4.70d, H(5') 4.5m,

H(6'a) 4.46dd ($J_{5',6'a}$ 3 Hz, $J_{6'a,6'b}$ 12.5 Hz), H(6'b) 4.24dd ($J_{5',6'b}$ 3.5 Hz), CH_3CO 2.25s, 2.08s, 1.94s and 1.90s.

Bromination of (5) under the conditions for preparation of corresponding natural compounds[7] gives per-O-acetylated 8-bromonucleoside (6) in 63% yield, UV, λ_{max}^{EtOH}, nm (ε): 263 (17,400); NMR (C^2HCl_3), ppm: H(2) 8.34s, H(3') 7.48d ($J_{3',4'}$ 5 Hz), NH_2 6.12s, H(4') 5.36dd ($J_{4',5'}$ 6 Hz), H(1'a) and H(1'b) 4.75t ($J_{1'a,1'b}$ 11 Hz), H(5') 4.6m, H(6'a) and H(6'b) 4.4–4.0m, CH_3CO 2.24s, 2.12s, 1.89s and 1.77s.

At the attempt to remove the acetyl groups, I have been faced with an unusual phenomenon. It turns out, that deblocking of bromonucleoside (6) with methanolic ammonia is accompanied with formation of a cyclonucleoside oxygen bridge. The desired anhydronucleoside (7) is obtained in 51% yield, m.p. 197–198° (from H_2O); mass spectrum, m/e 295 (M^+); UV, λ_{max}, nm (ε): pH 1 260 (15,500), pH 7 258 (16,500), pH 13 261 (15,000); CD, λ_{extr}, nm (Δε): pH 7 255 (+0.96), 267 (+0.84); NMR (^2H_2O), ppm: H(2) 8.09s, H(1'a) 5.55d ($J_{1'a,1'b}$ 10 Hz), H(1'b) 5.06d, H(3') 5.03d ($J_{3',4'}$ 4 Hz), H(4') and H(5') 4.4–4.1m, H(6'a) and H(6'b) ~3.9m.

It should be noted that formation of anhydrolinkages causes essential enhancement of the diastereotopic effect for the 1'-CH_2 group. The difference between chemical shifts of the H(1'a) and H(1'b) protons increases from 5–25 Hz to ~50 Hz. This phenomenon results from conformational rigidity of anhydronucleosides prepared and is well known in the case of related substances such as pyrimidine 6,5'-anhydronucleosides[8], purine 8,5'-anhydronucleosides[9a,b] and 1',3',4'-O-methylidynepsicofuranine[10].

Further investigations in this field, including crystallographic studies, are in progress.

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(6) All new compounds are homogenous from TLC and have satisfactory analytical data. Melting points are uncorrected. NMR-spectra are given at 100 MHz with tetramethylsilane or tert-butanol as internal references.

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