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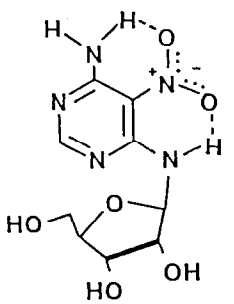
SYNTHESIS OF A NITRO GROUP CONTAINING RIBONUCLEOSIDE RELATED TO GUANOSINE

J. Claude ESPIE, M. France LHOMME, Claude MORAT and Jean LHOMME*

Laboratoire d'Etudes Dynamiques et Structurales de la Sélectivité, associé au CNRS,
Université Joseph FOURIER, BP 53X, 38041 GRENOBLE CEDEX, FRANCE

Summary : The α- and ß-anomers of the nitro group containing ribonucleoside 2 have been prepared in a three-step sequence. Both exhibit an intramolecular H-bond between the 4-NH and an oxygen atom of the nitro group.

Clitocine 1 was recently isolated from the mushroom Clitocybe inversa by Kubo et al.[1] and two independant syntheses have been reported[2,3]. Clitocine shows a strong insecticidal activity against the pink bollworm Pectinophora gossypiella[1]. It inhibits L 1210 cells in vitro and was found to be a substrate and inhibitor of adenosine kinase[2]. From the structural point of view, clitocine shows an interesting biogenetic relationship with adenosine and possesses a planar aglycon moiety with each oxygen atom of the nitro group hydrogen bonded to the two adjacent amino hydrogens (4-NH and 6-NH) as revealed by X-ray crystal data and NMR spectroscopy[2].



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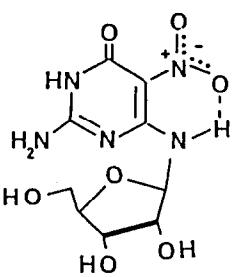
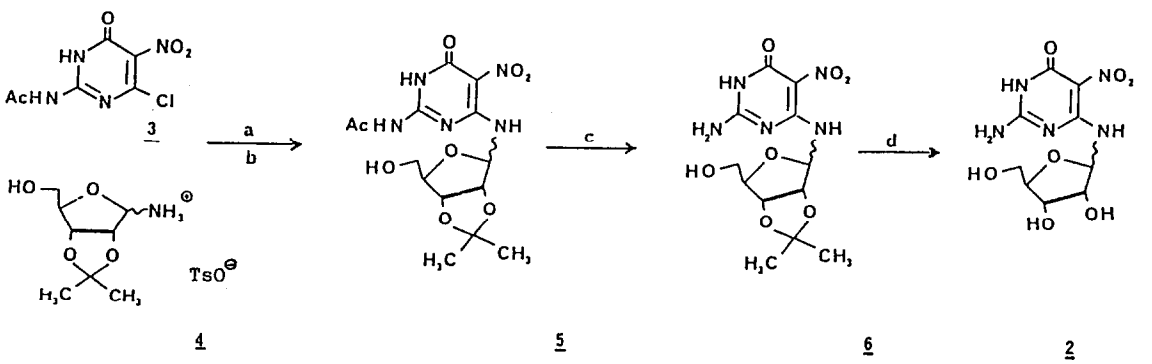


2β

These findings prompted us to synthesize the analog 2 which corresponds to guanosine. We report here the three step synthesis of the two anomers 2α and 2ß from readily available starting materials.

The synthesis involves building of the pyrimidine ring 3 with subsequent condensation with the protected ribofuranosylamine toluenesulphonate salt 4 leading to a mixture of α - and ß - anomers 5. The reaction conditions are quite critical for this condensation. The reaction can be run in dimethylformamide in the presence of triethylamine as previously reported[4]. However, the reproducibility and yields are improved when the reaction is conducted in absolute ethanol using sodium ethoxide as a base. Fractional recrystallization in water yields the two pure anomers[5,6] (60% yield ; α:ß ≃ 3:7) which are treated separately under identical conditions in the following deprotection steps. Reaction with hydrazine monohydrate in ethanol at room temperature leads to rapid and quantitative removal of acetyl group. Careful treatment of the resulting derivatives 6[7,8] with 95% trifluoroacetic acid in water at -10°C for 10 min gives the pure nucleosides 2α[9] and 2ß[10]. HPLC controls show that no noticeable anomerisation occurs during the deprotection steps.



a : EtONa, EtOH, 18 h ; b : crystallization of α-and ß-anomers ; c : 1eq NH_2 $NH_2.H_2O$, EtOH 15 min ; d : CF_3CO_2H 95%, -10°C, 10 min.

Assignment of α and ß configurations were based on a series of NMR experiments monitored on the protected derivatives 5[11]. These include homo and hetero NOE difference (only the ß isomer shows positive NOE enhancement on H_1' and H_4' when H_4' and H_1' are respectively pre-irradiated[12]). The Δδ shift value for isopropylidene methyl groups, often used for anomeric assignment[13], is not significant in these "exocyclic" nucleosides 5 and 6 (0.16 and 0.17 ppm for α and ß respectively). Configurations for compounds 6 and 2 were directly deduced from derivatives 5.

In clitocine 1 strong hydrogen bonding between the NO_2 group and the 4-amino

hydrogen has been reported to occur in the solid[2]. In solution this has been confirmed by ^1H NMR spectroscopy mainly on the basis of the large chemical shift of the 4-NH which appears as a doublet (7.7 Hz) at field unusually low ($\delta \simeq 9.3$ ppm)[1,2]. The same observation can be made for compounds 2, 5 and 6 in both the α and ß series. The 4-NH appears in the range of 9.58-10.23 ppm with well resolved coupling of ≃ 9 Hz with $H_{1'}$ denoting absence of exchange, whereas 2-NH_2, $OH_{2'}$, $OH_{3'}$ and $OH_{4'}$ show broad lines[12].

Consequently, nucleoside 2 exhibits a behaviour quite similar to the natural compound clitocine 1. Such nitro-containing nucleosides are quite rare. The "anomeric stability" observed during the deprotection steps of 5 is remarkable. It may be related to the strong intramolecular hydrogen bonding which in addition should favour a planar "pseudo bicyclic" structure in the aglycon part of the nucleosides. Structural and biological studies of these compounds are in progress.

Acknowledgment :

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5- 2-Acetylamino-5-nitro-6-((2',3'-O-isopropylidene- α -D-ribofuranosyl)amino)-4-pyrimidinone-3H (5α) : 20% ; mp : 230°C ; ^1H NMR ($DMSOd_6$) : 11.60 (s, 1H), 9.91 (d, 1H), 6.05 (m, 1H), 4.99 (t, 1H), 4.81 (m, 2H), 4.03 (td, 1H), 3.49 (m, 2H), 2.21 (s, 3H), 1.51 (s, 3H), 1.35 (s, 3H) ppm ; ^{13}C NMR ($DMSOd_6$) : 174.57, 158.28, 151.39, 151.15, 113.21, 112.27, 81.88, 81.79, 78.98, 62.14, 25.85, 24.49, 24.30 ppm ; IR (Nujol) : 3540, 3380, 3320, 3200, 1685, 1615, 1580, 1530, 1500 cm^{-1} ; MS (FAB^+) : 386 $(M+H)^+$; UV (ethanol) : 332.9 (1200), 282.0 (5500) 237.4 (16500), 214.7 (23600)nm.

6- 2-Acetylamino-5-nitro-6-((2',3'-O-isopropylidene- β -D-ribofuranosyl)amino)-4-pyrimidinone-3H (5ß) : 42% ; mp : 202-203°C ; ^1H NMR ($DMSOd_6$) : 11,55(s, 1H), 10.16(d, 1H), 6.21(dd, 1H), 5.49(t, 1H), 4.85 (dd,1H), 4.70(dd, 1H), 4.23(td, 1H), 3.56(m, 2H), 2.20(s, 3H), 1.45 (d, 3H), 1.28(d, 3H) ppm ; ^{13}C NMR ($DMSOd_6$) : 174.27, 157.30, 154.01, 150.44, 112.60, 111.47, 88.0, 86.60, 86.05, 82.09, 60.10, 26.36, 24.45, 23.88 ppm ; IR (Nujol) : 3320, 1740, 1680, 1520 ; MS(EI) : 385 $(M)^+$, 370, 354, 327, 242, 213 ; UV (ethanol) : 335.0(11800), 280.0(5400), 240.0(17100), 212.0(35600)nm ; $C_{14}H_{19}O_8N_5$. Calcd % : C, 43.64 ; H, 4.97 ; N, 18.18. Found % : C, 43.71 ; H, 5.01 ; N, 17.97.

7- 2-Amino-5-nitro-6-((2',3'-O-isopropylidene- α -D-ribofuranosyl)amino)-4-pyrimidinone-3H (6α) : 75% ; mp : 292-306°C ; ^{1}H NMR ($DMSOd_6$) : 10.76 (s, 1H), 9.94 (d, 1H), 6.03 (m, 1H), 4.90 (t, 1H), 4.78 (m, 2H), 3.98 (t, 1H), 3.48 (m, 2H), 1.49 (s, 3H), 1.32 (s, 3H) ppm ; ^{13}C NMR ($DMSOd_6$) : 158.77, 156.12, 154.38, 112.23, 111.08, 81.89, 81.73, 81.57, 72.02, 62.12, 25.91, 24.58 ppm ; IR (Nujol) : 3460, 3320, 1700, 1650, 1600, 1575, 1555, 1503 cm^{-1} ; MS (FAB^-) : 342 $(M-H)^-$; UV (ethanol) : 327.2 (13900), 237.4 (16800), 210.8 (23100)nm.

8- 2-Amino-5-nitro-6-((2',3'-O-isopropylidene-ß-D-ribofuranosyl)amino)-4-pyrimidinone-3H (6ß) : 50% ; mp : 260-268°C ; ^{1}H NMR ($DMSOd_6$) : 10.70 (s, 1H), 10.10 (d, 1H), 6.16 (dd, 1H), 5.44 (t, 1H), 4.80 (dd, 1H), 4.64 (dd, 1H), 4.17 (t, 1H), 3.51 (m, 2H), 1.42 (s, 3H), 1.26 (s, 3H) ppm ; ^{13}C NMR ($DMSOd_6$) : 158.22, 156.30, 154.06, 111.54, 110.60, 87.90, 86.37, 86.25, 82.27, 62.33, 26.57, 24.35 ppm ; IR (nujol) : 3460, 3320, 1680, 1650, 1560, 1500 cm^{-1} ; MS (FAB^-) : 342 $(M-H)^-$, (FAB^+) : 344 $(M+H)^+$; UV (ethanol) : 328.1 (13600), 276.5 (5200), 237.9 (11000), 212.2 (23000)nm.

9- 2-Amino-5-nitro-6-((- α -D-ribofuranosyl)amino)-4-pyrimidinone-3H (2α) : 46% ; mp : 256-270°C ; ^{1}H NMR ($DMSOd_6$) : 10.73 (s, 1H), 10.18 (d, 1H), 8.0 (s, 1H), 6.6 (s, 1H), 5.94 (q, 1H), 5.42 (d, 2H), 5.1 (d, 1H), 4.6 (t, 1H), 4.03 (q, 1H), 3.86 (q, 1H), 3.79 (m, 1H), 3.39 (m, 2H) ppm ; ^{13}C NMR ($DMSOd_6$) : 159.09, 156.25, 154.21, 110.87, 82.80, 80.31, 71.25, 70.02, 61.53 ppm ; IR (nujol) : 3450, 3200, 1710, 1630, 1570, 1500 ; MS (FAB^+, HR) : 304,0943 $(M+H)^+$; UV (ethanol) : 324.6 (4200), 278.7 (4600), 238.0 (11200), 206.8 (29300)nm.

10 - 2-Amino-5-nitro-6-((-ß-D-ribofuranosyl)amino)-4-pyrimidinone-3H (2ß) : 93% ; mp : 260°C ; ^{1}H NMR ($DMSOd_6$) : 10.76 (s, 1H), 9.58 (d, 1H), 8.0 (s, 1H), 6.6 (s, 1H), 5.73 (q, 1H), 5.1 (t, 1H), 4.9 (s, 2H), 3.96 (t, 1H), 3.90 (t, 1H), 3.72 (q, 1H), 3.40 (m, 2H) ppm ; ^{13}C NMR ($DMSOd_6$) : 159.21, 156.15, 154.20, 110.80, 84.97, 84.14, 74.94, 70.33, 61.10 ppm ; IR (nujol) : 3480, 3400, 3300, 3200, 1740, 1580, 1530, 1505 cm^{-1} ; MS (FAB^-) : 302 $(M-H)^-$; UV (ethanol) : 328.2 (17800), 277.9 (4600), 237.3 (15300), 211.5 (21000) nm ; $C_9H_{13}N_5O_7$, 0.25 H_2O : Calcd.% : C, 35.13 ; H, 4.42 ; N, 22.76 ; O, 37.69. Found % : C, 35.05 ; H, 4.55 ; N, 23.09 ; O, 37.38.

11- All the ^{1}H NMR spectra were run on Bruker AM 300 at 300.13 MHz in $DMSOd_6$ (≃ 50 mMole/l) at 310°K in a 5 mm $^{1}H/^{13}C$ dual probe.

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