Tetrahedron Letters No. 38, pp 3271 - 3274, 1975, Pergamon Press. Printed in Great Britain.

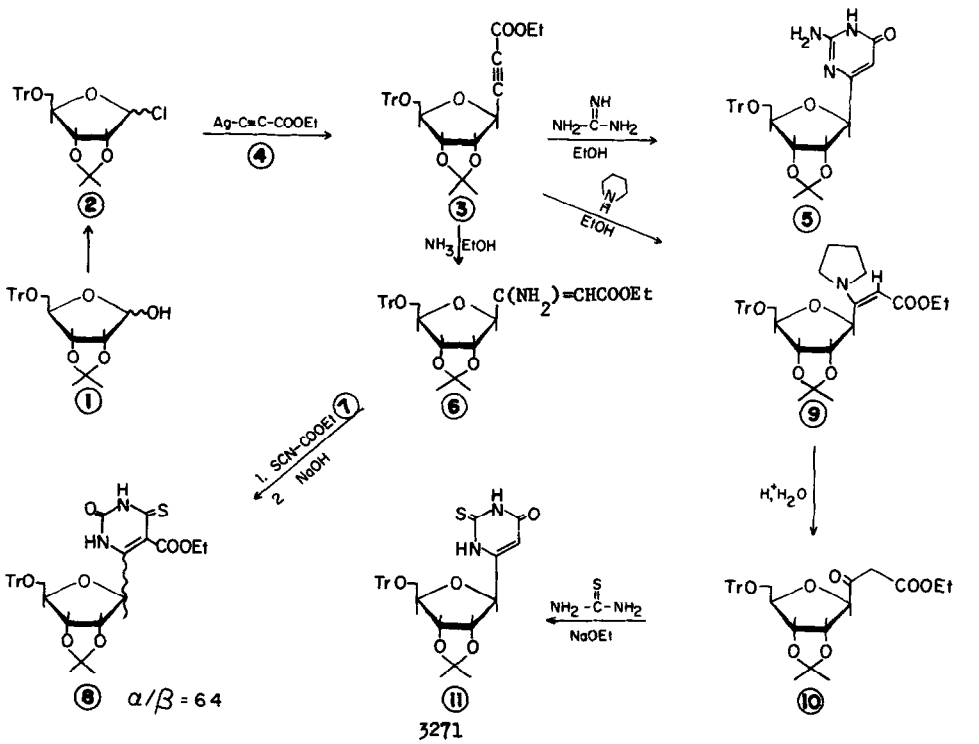
NUCLEOSIDES XCIII. SYNTHESIS OF 6-β-D-RIBOFURANOSYL-PYRIMIDINES (A NEW CLASS OF PYRIMIDINE C-NUCLEOSIDES) [1]

Steve Y-K. Tam, Federico G. De Las Heras, Robert S. Klein and Jack J. Fox

Laboratory of Organic Chemistry, Sloan-Kettering Institute for Cancer Research, Sloan-Kettering Division of Graduate School of Medical Sciences, Cornell University, New York, N.Y. 10021

(Received in USA 27 June 1975; received in UK for publication 12 August 1975)

Recent reports have dealt with the preparation of functionalized C-glycosyl compounds [2] as synthetic intermediates for the preparation of naturally occurring C-nucleosides and their analogues [2a,d-g]. As part of our general program on the synthesis of C-nucleosides, we have prepared the new C-glycosyl derivative, ethyl 3-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)propiolate (3) [3], bearing an α,β-acetylenic ester function at C-1 of the ribose moiety. Its preparation and subsequent facile transformation into pyrazole- and triazole-C-nucleosides by means of 1,3-dipolar cycloaddition reactions are discussed in detail in a separate publication [4]. We now report the synthesis from 3 of a new class of pyrimidine C-nucleosides in which the sugar is attached to the C-6 of the base. The synthetic routes utilize two other key intermediates, 6



and 10, belonging to two important classes of organic compounds, namely enamines and β-keto esters.

After chromatographic separation from the α-isomer, compound 3 was obtained in 36% yield from the reaction of the silver acetylide of ethyl propiolate (4) (0.21 mole) with the ribosyl chloride 2. The latter was prepared in situ from the reaction of 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose (1) (0.1 mole) with Ph_3P (0.15 mole) and CCl_4 (0.2 mole) in CH_3CN (250 ml) [4,5]. For 3: pmr ($CDCl_3$) δ 1.19 (3,t,$CO_2CH_2CH_3$), 1.30 and 1.50 (6,2s,CMe_2), 3.29 (2,m, H-5', H-5"), 4.13 (2,q,$CO_2CH_2CH_3$), 4.33 (1,m,H-4'), 4.62 (1,dd,$J_{2',3'}$ = 5.8Hz, $J_{3',4'}$ = 1.8Hz, H-3'), 4.76 (1,d, $J_{1',2'}$ = 2.8Hz, H-1'), 4.84 (1,dd,H-2'), 7.20-7.53 (15,m,trityl). For the α-isomer of 3: pmr ($CDCl_3$) δ 1.30 (3,t,$CO_2CH_2CH_3$) 1.35 and 1.56 (6,2s,CMe_2), 3.10 (1,dd,$J_{4',5'}$ = 3.1Hz, $J_{5',5"}$ = 10.2 Hz, H-5'), 3.43 (1,dd,$J_{4',5"}$ = 3.0Hz, H-5"), 4.24 (3,m,$CO_2CH_2CH_3$,H-4'), 4.70 (1,d,$J_{2',3'}$ = 6.0Hz, $J_{3',4'} \cong 0$, H-3'), 4.96 (1,dd,$J_{1',2'}$ = 4.7Hz, H-2'), 5.18 (1,d,H-1'), 7.27-7.38 (15,m, trityl). The anomeric configuration assignments are based on the observation of the lower chemical shift of H-1' of the α-isomer relative to that of the β-isomer [6].

Treatment of 3 with 1.1 equivalent of guanidine in ethanol at room temperature for 7 hr. afforded, after crystallization, a 55% yield of the C-nucleoside 5: m.p. 224-225° dec: λ_{max}^{EtOH} 287.5 nm, $^{pH\ 1}$ 259 nm, $^{pH\ 12}$ 276 nm (similar to the spectrum of a sample of 6-methyl-isocytosine); pmr (DMSO-d_6) δ 1.23 and 1.45 (6,2s,CMe_2), 3.10 (2,m,H-5',H-5"), 4.11 (m,1,H-4'), 4.42 (1,dd, $J_{2',3'}$ = 6.4Hz, $J_{3',4'}$ = 4.3Hz, H-3'), 4.52 (1,d,$J_{1',2'}$ = 3.0Hz, H-1'), 4.69 (1,dd,H-2'), 5.74 (1,s,H-5), 6.61 (2, broad s, NH_2), 7.28-7.37 (15,m,trityl), 10.72 (1, broad s, NH).

Compound 6 was obtained in near quantitative yield by treatment of 3 with saturated ethanolic ammonia for two hr at 105° in a bomb: m.p. 117-118°; pmr ($CDCl_3$) δ 1.26 (3,t,$CO_2CH_2CH_3$), 1.33 and 1.54 (6,2s,CMe_2), 3.27 (1,dd,$J_{4',5'}$) = 4.1 Hz, $J_{5',5"}$ = 10.5Hz, H-5'), 3.46 (1,dd,$J_{4',5"}$ = 3.4Hz H-5"), 4.12 (2,q,$CO_2CH_2CH_3$), 4.23 (1,m,H-4'), 4.40 (1,m,H-3'), 4.62-4.65 (2,m,H-2',H-1'), 4.71 (1,s,H-2,exchangeable with NaOD), 6.71 (2, broad s, NH_2), 7.25-7.48 (15,m,trityl). Reaction of 6 with 1.2 equivalent of ethoxycarbonyl isothiocyanate (7) [7] in CH_3CN at room temperature for 14 hr, followed by a brief treatment with aqueous NaOH gave an α,β mixture (α/β = 6.4 determined by pmr analysis) of the 5-carbethoxy-4-thiouracil-C-nucleoside 8 in a 61% total yield [8]; λ_{max}^{EtOH}, $^{pH\ 5}$ 335 nm, $^{pH\ 9}$ 348 nm (similar to the spectrum of a sample of 6-methyl-4-thiouracil). Partial separation by chromatography afforded a pure sample of each isomer. PMR ($CDCl_3$) data for the α-isomer of 8: δ 1.18 (3,t,$CO_2CH_2CH_3$), 1.29 and 1.43 (6,2s,CMe_2), 3.16 (1,dd,$J_{4',5'}$ = 2.5Hz, $J_{5',5"}$ = 10.4Hz,H-5'), 3.52 (1,dd,$J_{4',5"}$= 2.0Hz,H-5"), 4.03-4.39 (3,m,$CO_2CH_2CH_3$,H-4'), 4.69 (1,d,$J_{2',3'}$ = 5.8Hz, $J_{3',4'}$ = 0,H-3'), 5.22 (1,dd,$J_{1',2'}$ = 4.6 Hz,H-2'), 5.40 (1,d,H-1'),

7.25-7.39 (15,m,trityl), 8.99 and 10.15 (2, 2 broad s, NH's); for the β-isomer: δ 1.35 and 1.55 (6,2s,CMe_2), 1.37 (3,t,$CO_2CH_2\underline{CH_3}$), 3.40 (2,m,H-5',H-5''), 4.25-4.46 (3,m,$CO_2\underline{CH_2}CH_3$,H-4'), 4.70 (1,m,H-3'), 4.81-4.95 (2,m,H-2',H-1'), 7.26-7.38 (15,m,trityl), 8.78 and 9.37 (2, 2 broad s, NH's). The configurational assignments of 8 made on the basis of the relative chemical shifts of H-1' signals are also consistent with the large difference of the Δδ values of the isopropylidene methyl signals [9] in both isomers. The formation of 11 by the other possible mode of cyclization (attack by NH_2 on the isothiocyanate) were not observed. This result (formation of 8) demonstrates the enamine character of 6, in parallel with previous observations on similar systems [7].

Compound 11 was prepared by a route which should be applicable to the synthesis of other 6-ribosyl-pyrimidines. Thus reaction of 3 with 1.1 equivalent of pyrrolidine in ethanol at 0°C gave a 96% yield of the enamine 9: m.p. 118.5-120°; λ_{max}^{EtOH} 293 nm; pmr ($CDCl_3$) δ 1.21 (3, t,$CO_2CH_2\underline{CH_3}$), 1.35 and 1.59 (6,2s,CMe_2), 1.78 and 3.38 (4 each, m, pyrrolidine H's), 3.46 (2,m, H-5',H-5''), 3.93-4.12 (3,m,$CO_2\underline{CH_2}CH_3$,H-4'), 4.61 (1,s,H-2), 4.78-5.10 (2,m,H-3',H-2'), 6.35 (1,d,$J_{1',2'}$ = 4.8 Hz,H-1'), 7.22-7.48 (15,m,trityl). Hydrolysis of 9 with Dowex 50 (H^+) resin in aqueous ethanol (followed to completion by the disappearance of its uv absorption at 293 nm) afforded a quantitative yield of the β-keto ester 10, $\lambda_{max}^{pH\ 12}$ 276 nm; pmr ($CDCl_3$) δ 1.18 (3,t, $CO_2CH_2\underline{CH_3}$), 1.33 and 1.54 (6,2s,CMe_2), 3.25 (2,m,H-5',H-5''), 3.49 and 3.69(2,2d,geminal coupling 16.2Hz,H-2's, exchangeable with NaOD), 4.08 (2,q,$CO_2\underline{CH_2}CH_3$), 4.26 (1,m,H-4'), 4.47-4.57 (2,m,H-3',H-1'), 4.89 (1,dd,$J_{2',3'}$ = 6.4 Hz, $J_{1',2'}$ = 4.1 Hz,H-2'), 7.21-7.52 (15,m,trityl). Minor signals of the enol-tautomer: δ 1.26 (t,$CO_2CH_2\underline{CH_3}$), 4.18 (q,$CO_2\underline{CH_2}CH_3$), 4.47-4.57 (m,H-3',H-1'), 4.77 (dd, $J_{2',3'}$ = 6.2 Hz, $J_{1',2'}$ = 4.1 Hz,H-2'), 5.44 (d, $J_{2,1'}$ = 1.0Hz,H-2).

Reaction of 10 at room temperature with an ethanolic solution of thiourea (5 equivalents) which had been previously heated with sodium ethoxide (1 equivalent) afforded the 2-thiouracil-C-nucleoside 11 in 74% yield. For 11: m.p. 119-120.5°; λ_{max}^{EtOH} 275 nm, $^{pH\ 5}$ 275 nm, $^{pH\ 10}$ 315 nm (similar to the spectrum of a sample of 6-methyl-2-thiouracil); pmr (DMSO-d_6) δ 1.27 and 1.49 (6,2s,CMe_2), 3.17 (2,m,H-5',H-5''), 4.10 (1,m,H-4'), 4.54 (1,dd, $J_{3'4'}$ = 4.5Hz, $J_{2',3'}$ = 5.0Hz, H-3'), 4.69 (1,d,$J_{1',2'}$ = 3.6Hz,H-1'), 4.78 (1,dd,H-2'), 5.98 (1,s,H-5), 7.36 (15,m,trityl), 12.44 (2, broad s, NH's).

The assignment of the geometric configuration of 9 is tentative and is based on the reported *cis* mode of addition of secondary amines to α,β-acetylenic esters [10].

The assignment of β-configuration to 5 and 11 is based on the observation of large Δδ values of their isopropylidene methyl groups signals (> 0.20 ppm) [9] in the PMR spectra and on their synthetic relationship to parent compound 3.

The synthesis of other members of this new class of pyrimidine C-nucleosides, notably the uracil and cytosine derivatives, are in progress.

Proper elemental analyses have been obtained for all new compounds.

References

1. This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U.S. Public Health Service (Grant No. CA 08748); Fellowship Montgomery Fund (S. Y-K. T.) and Fellowship from "Program of Cultural Cooperation between U.S.A. and Spain" (F.G.D.L.H.)

2. For recent examples see below and references therein: a) H. Ohrui and J. J. Fox, Tetrahedron Lett., 1951 (1973); b) S. Hanessian and A.G. Pernet, Can. J. Chem., 52, 1266 (1974); c) J. G. Buchanan, A.R. Edgar, and M.J. Power, J. Chem. Soc. Perkin I, 1943 (1974); d) H.P. Albrecht, D.B. Repke, and J. G. Moffatt, J. Org. Chem., 39, 2176 (1974); e) W.J. Gensler, S. Chan, and D.B. Ball, J. Amer. Chem. Soc., 97, 436 (1975); f) G. Just and M. Ramjeesingh, Tetrahedron Lett., 985 (1975); g) C.K. Chu, K.A. Watanabe, and J.J. Fox, J. Heterocycl. Chem., in press.

3. The chosen nomenclature in our opinion is to be understood more easily than the alternative: Ethyl 4,7-anhydro-5,6-O-isopropylidene-8-O-trityl-D-allo-oct-2-ynoate.

4. F.G. De Las Heras, S.Y-K. Tam, R.S. Klein and J. J. Fox, submitted for publication.

5. R.S. Klein, H. Ohrui and J. J. Fox, J. Carbohydr. Nucleosides, Nucleotides, 1, 265 (1974).

6. Similar arguments have been used in the cases of nucleosides [6a] and C-glycosyl compounds [6b] a) L. B. Townsend, in "Synthetic Procedures in Nucleic Acid Chemistry", Vol. 2, W.W. Zorbach and R.S. Tipson, Eds., Wiley Interscience, New York, 1973, p. 330; b) H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S.K. Byram, J. Amer. Chem. Soc., in press. The authors are indebted to Dr. Moffatt of the Institute of Molecular Biology, Syntex Research, Palo Alto, Calif. for access to the manuscript prior to publication.

7. a) J. Goerdeler and H. Horn, Ber., 96, 1551 (1963); b) J. Goerdeler and D. Wieland, Ber., 100, 47 (1967); c) R. Esmail and F. Kurzer, Synthesis, 301 (1975).

8. Inversion of configuration at C-1' probably occurs during the base treatment step in which abstraction of H-1' of the intermediate 7 would afford a carbanion highly stabilized by conjugation to two acyl groups. Further experiments are underway to elucidate this point.

9. J.L. Imbach and B.L. Kam, J. Carbohydr. Nucleosides, Nucleotides, 1, 271 (1974).

10. E. Winterfeldt in "Newer Methods of Preparative Organic Chemistry" Vol. VI, Foerst Ed., Verlag Chemie GmbH, 1971.