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NOTE

Facile Synthesis of Unusual Pyrimidine Nucleosides

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Two novel unusual pyrimidine nucleosides, *viz.*, 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-5-iodo-6-methyluracil (**1**) and 1-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-5-iodo-6-methyluracil (**2**) have been prepared using $HgCl_2/TiCl_4$ method and characterized.

Key Words: 5-iodo-6-methyluracil, 1,2,3,4,6-tetra-O-acetyl-α-D-glucosylchloride, 1,2.3,4,6-penta-O-acetyl-β-D-galactopyranose, $HgCl_2$, Biological activities.

Substituted pyrimidine nucleosides[1–7] have shown different biological activities. Some of the synthetic compounds[8] have recently been studied for their anti-bacterial and antifungal properties. Motoo *et al.*[9] have patented β-D-ribofuranosyl pyridopyrimidinedione nucleoside analogues as potential anticancer agents. A number of synthetic methods[10–19] are now available in literature for the preparation of various nucleoside derivatives. Two procedures are generally used for preparing synthetic nucleosides. Procedure-I involves coupling of nucleobase with acylated sugar halides and Procedure-II deals with the condensation of O-acyl or O-benzoyl sugar derivatives with nucleobases resulting in higher yields of nucleosides. It is pertinent to mention here that titanium tetrachloride[13] as a catalyst eliminates the need for separate preparation of O-acyl or O-benzoyl sugar halides. Several purine nucleosides have been prepared by coupling of an O-acylated sugar halide with a metallic salt of purine involving an acidic catalyst[17, 19]. The present paper reports the synthesis of unusual glucopyranosyl-5-iodo-6-methyluracil and galactopyranosyl-5-iodo-6-methyluracil as possible biologically active compounds.

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-5-iodo-6-methyluracil (1)

The compound was prepared by coupling of nucleobase with 1-chloro acetylated sugar derivative. 5-Iodo-6-methyluracil (1.008 g, 4 mmol) was added to boiling 75% ethanol (10 mL). NaOH (2 N, 5 mL) was added slowly to the mixture. A solution of $HgCl_2$ (1.118 g, 4.12 mmol) in ethanol (95%) was added to it dropwise. The mixture was stirred for 30 min, water (10 mL) was added, allowed to cool and filtered to afford chloromercury derivative of the pyrimidine base in 86% yield. To the solution of derivative (3 mmol) in dry xylene (15 mL) was added a solution of 2,3,4,6-tetra-O-acetyl-α-D-glucosyl chloride (1.099 g, 3 mmol) in dry xylene (10 mL). The content was refluxed for 2.5 h and subjected to hot filtration. The solid residue obtained after evaporation of the filtrate was dissolved in $CHCl_3$ and washed with KI (30%) in water, dried over anhydrous $MgSO_4$ and evaporated to dryness. Again the residue was dissolved in $CHCl_3$ and absolute MeOH was added to the solution. The product was filtered and recrystallized from alcohol in 74% yield.

^{1}H NMR (300Mhz, DMSO-d_6): δ = 1.83 (s, 3H, 6-CH_3), 4.89 (m, 3H, H-2′,3′,4′), 4.72 (m, 1H, H-1′), 4.02–3.50 (m, 3H, CH_2O and H-5′), 2.05, 2.0, 1.92 (3s, 12H, 4Ac); 13C NMR (90Mhz, $CDCl_3$): δ = 148.5 (C-2), 161.2 (C-4), 150.1 (C-5), 155.6 (C-6), 62.3 (C-1′), 69.8 (C-2′), 66.2 (C-3′), 65.2 (C-4′), 64.8 (C-5′), 63.8 (C-6′), 169.2 (=CO), 14.6 (CH_3); HRMS-FAB: m/z $[M + H]^+$ calcd. for $C_{19}H_{23}N_2O_{11}I$: 583.3059; found: 583.3061.

1-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-5-iodo-6-methyluracil (2)

Compound **2** was prepared by reacting 5-iodo-6-methyluracil (0.756 g, 3 mmol) with 1,2,3,4,6-penta-O-acetyl-β-D-galactopyranose (1.17 g, 3 mmol). Dry acetonitrile (20 mL) was added to the above mixture and $TiCl_4$ (0.5 M) solution was added to it dropwise at 0°C. The solvent was evaporated under reduced pressure and the solution was poured into saturated solution of $NaHCO_3$ (18 mL) and extracted thrice with $CHCl_3$ (7 mL). The chloroform extracts were washed with water, dried and solvents evaporated. The residue was recrystallized from ethanol to afford the pure product in 70% yield. The deacetylation of protected nucleoside could be performed with methanolic ammonia or methanolic sodium hydroxide to afford free nucleoside.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.78 (s, 3H, 6-CH_3), 4.45–4.77 (m, 3H, H-2′,3′,4′), 4.74–4.20 (m, 2H, H-1′ and CHO), 4.19–3.70 (m, 3H, CH_2O and H-5′), 2.00–1.88 (m, 12H, 4Ac); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 149.1 (C-2), 161.8 (C-4), 150.0 (C-5), 155.2 (C-6), 62.0 (C-1′), 69.2 (C-2′), 66.0 (C-3′), 64.9 (C-4′), 64.2 (C-5′), 63.7 (C-6′), 168.8 (=CO), 14.3 (CH_3). HRMS-FAB: m/z $[M + H]^+$ Calcd. for $C_{19}H_{23}N_2O_{11}$: 583.3059; Found: 583.3060

Two nucleosides (**1**) and (**2**) have been prepared by coupling of nucleobase with 1-chloro acetylated sugar derivative and by condensation of nucleobase with 1-O-acetyl sugar derivative. 5-Iodo-6-methyluracil was reacted with ethanolic solution of mercuric chloride in alkaline medium to afford chloromercury derivative of the pyrimidine base in 86% yield. The derivative was reacted with 2,3,4,6-tetra-O-acetyl-α-D-glucosylchloride in dry xylene. The content was refluxed for 2.5 h and subjected to hot filtration. The product (**1**) was filtered and recrystallised from alcohol in 74% yield.

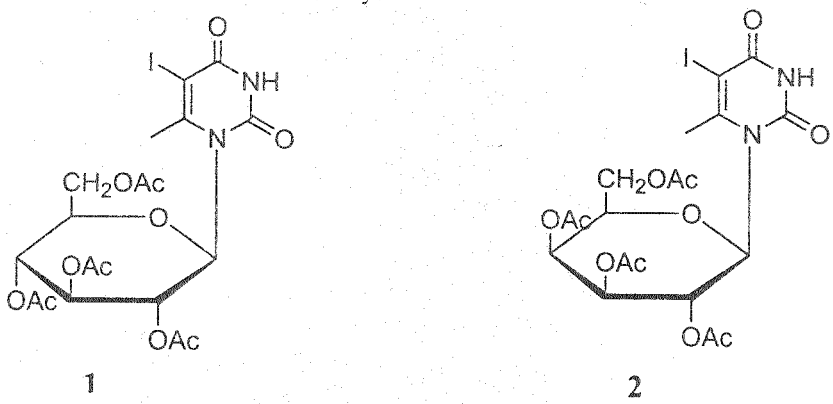

Fig. 1.

Similar procedure with slight modifications was used for compound (**2**) by reacting 5-iodo-6-methyluracil with 1,2,3,4,6-penta-O-acetyl-β-D-galactopyranose in dry acetonitrile following dropwise addition of titanium chloride solution at

0°C. The solvent was evaporated under reduced pressure and the solution was poured into saturated solution of sodium bicarbonate, extracted with chloroform. The residue was recrystallized from ethanol to afford the pure product (2) in 70% yield. Selected physicochemical and spectroscopic data of the compounds (1) and (2) have been presented. The deacetylation of protected nucleosides could be performed with methanolic ammonia or methanolic sodium hydroxide to afford the free nucleosides.

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REFERENCES

1. H. Iwamura, S. Murakami, K. Koshimizu and S. Matsubara, *J.Med.Chem.*, **28**, 577 (1985).
2. H. Yuki and Y.Naka, *Japan Kokai.*, **76**, 139, (1976), *Chem. Abstr.*, **84**, 121 (1976).
3. T.H. Althius, P.F. Moore and H.J. Hess., *J. Med. Chem.*, **22**, 44 (1979).
4. N.L. Colbry, E.F. Elslager and L.M. Werbel., *J. Heterocyclic Chem.*, **21**, 1521 (1984).
5. C.G. Dave, P.R. Shah, G.K. Shah, P.S. Pandya and K.C. Dave, *Indian J. Pharm. Sci.*, **48**, 75 (1986).
6. F. Corelli, S. Massa, G. Stefancieh., M. Artico, S.Panico and N. Simonett., *Farmaco (Sci.)*, 39, 95 (1984).
7. D. Bouzard, P. Dicesare, M. Essiz, J.P. Jacquet, J.R. Kicchel, P. Remuzon, A. Weber, T. Oki and M. Mahyoshi. *J. Med. Chem.*, 33, 1344 (1990).
8. A.K. Sharma, A.K. Yadav and L. Prakash, *Indian J. Chem.*, **34B**, 740 (1995).
9. H. Motoo, P. Yoshio, R.M. Ohanj, I. Ichiro, M. Yoshihisa, K. Tokuo and O. Haruo, *Chem. Abstr.*, **112**, 7859 (1990).
10. M.J. Robins, W.A. Bowles and R.K. Robins., *J. Am. Chem. Soc.*, **86**, 1251 (1964).
11. P. Kohn, L. M. Lerner and B. D. Kohn., *J. Org. Chem.*, **32**, 4076 (1967).
12. W.T. Ping and J.M. Williams, *J. Chem. Soc. Perkin Trans. I*, **6**, 1199 (1984).
13. D.H. Murray and J. Prokop. *J. Pharm.*, **54**, 1468 (1965).
14. B.R. Baker and R.E. Schayb., *J. Am. Chem. Soc.*, **77**, 5900 (1955).
15. R.U. Lemieux, *Methods Carbohyd. Chem.*, **22**, 23 (1963).
16. T. Mukaiyama, T. Takashima, M. Katsurada and H. Aizawa, *Chem. Lett.*, **4**, 533 (1991).
17. A. F. Sayed and Ahmad, *Indian J. Chem.*, **33B**, 69 (1994).
18. M. Casey, C.J. Moody and C.W. Rees. *J. Chem. Soc. Perkin Trans. I.*, **8**, 1933 (1984).
19. A.F. Sayed Ahmad, *International J. Chem.*, **4**, 33 (1993).

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