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SYNTHESIS OF 4-(2,4-DIOXO-1H,3H-PYRIMIDYL-5-)-6-METHYL-3,5-DIOXO-2-H-1,2,3-TRIAZINE AND ITS GLYCOSIDE DERIVATIVES

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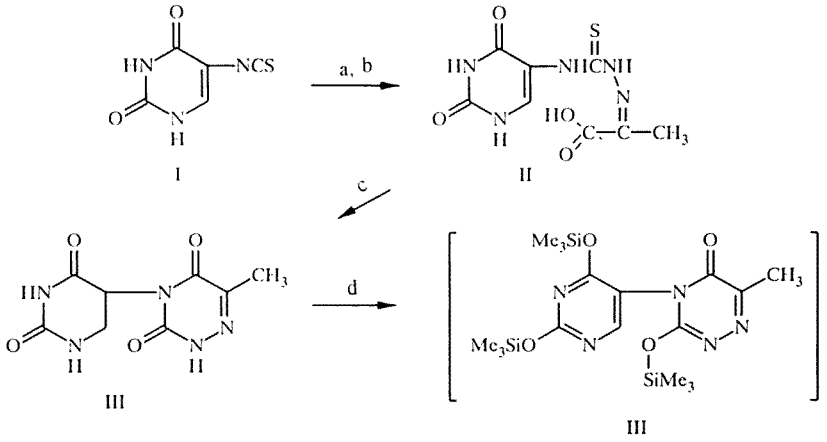
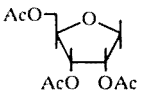
Azapyrimidine nucleosides and 5-substituted 2′-desoxyuridines are known inhibitors of the biosynthesis of pyrimidine nucleotides [1, 2]. In this connection it was expedient to synthesise a "coupled" pyrimidyl-azapyrimidyl heterocycle — $N_{(3)}$-(uracilyl-5)-6-azathymine (III) and its nucleoside derivatives and to study their biological properties.

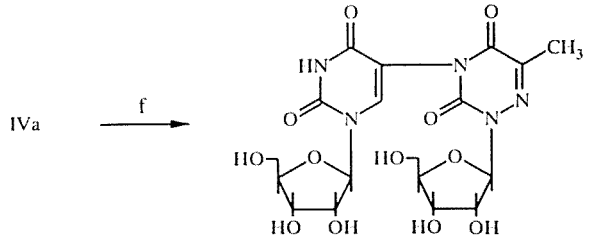
The synthesis of 4-(2,4-dioxo-1H,3H-pyrimidyl-5-(6-methyl-3,5-dioxo-2H-1,2,4-triazine (III) began with the construction of the triazine heterocycle on the uracil ring by preparing and cyclising the pyruvic acid thiosemicarbazone.



I, II, III, III, IV

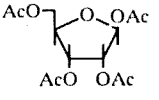
IVa R = H; IV b R =





IVa, Va

a $NH_2NH_2 \cdot H_2O$; b CH_3COCO_2Na/H^+; c CH_3I; d $(Me_3Si)_2NH/Me_3SiCl$;

e  /$SnCl_4$; f NH_3/MeOH

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Hydrazine hydrate (96%, 1 cm^3) was added to a solution of uracil 5-isothiocyanate (I) (10 mmol) [3] in water (100 cm^3) containing triethylamine (2.8 cm^3). The mixture was kept for 14-16 h, then neutralised to pH 6 with hydrochloric acid, sodium pyruvate (12 mmol) was added and the mixture stirred at 50°C for 1-1.5 h. After acidification to pH 2 with hydrochloric acid the $N_{(1)}$-(uracilyl-5)thiosemicarbazone of pyruvic acid (II) was obtained (2.4 g, 88%) as white crystals, mp 219-221°C (from water). UV spectrum (water): λ_{max} 280 nm, ε 13,500.

Compound II was cyclised by a known method [4]. Thiosemicarbazone I (2 mmol) and methyl iodide (0.6 cm^3) in water (30 cm^3) were boiled for 3-3.5 h, the solvent evaporated in vacuum, the residue evaporated with ethanol and crystallised from water to give $N_{(3)}$-(uracilyl-5)-6-azathymine (III) (60%) as a white powder which did not melt below 340°C. TLC (butanol–acetic–acid water, 5:2:3): R_f 0.73. UV Spectrum (water): λ_{max} 264 nm, ε 13,100; (0.1 M NaOH) λ_{max} 289, ε 10,980. ^{1}H NMR Spectrum (DMSO-d_6, 200 MHz): 12.44 (1H, s, $N_{(3')}$-H), 11.60 (1H, s, $N_{(1)}$-H), 11.32 (1H, br.s, $N_{(1')}$-H), 7.37 (1H, s, 6'-H), 2.12 ppm (3H, s, 5-CH_3).

The structure of compound III was confirmed by the considerable intensity of the UV absorption maximum, explained by the superposition of the absorption bands of both heterocycles, and the bathochromic shift and decrease in intensity of the absorption band in alkaline medium which is associated with the absorption of the anionic form of the uracilyl (λ_{max} 285, ε 5910) [4] and the $N_{(3)}$-substituted azathymine residues (λ_{max} 296, ε 5840) [6].

Glycosides of compound III were prepared analogously to a known method [7]. Trimethylchlorosilane (3 cm^3) was added dropwise over 1.5-2 h to a boiling suspension of compound III (2 mmol) in hexamethyldisilazane (30 cm^3). The solvent was removed in vacuum and the residue was dissolved in absolute dichloroethane (40 cm^3), ribofuranose tetracetate (4 mmol) was added, and then tin tetrachloride (3.4 mmol) in dichloroethane (5 cm^3) was added dropwise over 1 h at 70°C. The mixture was kept at 20°C for 1 h and then finely powdered $NaHCO_3$ (2-3 g) was added with vigorous stirring. The solution was filtered and the filtrate washed with saturated aqueous $NaHCO_3$ and water. The organic layer was dried with Na_2SO_4, evaporated to dryness, and the residue was purified by chromatography on a silica gel column (40 x 100 μk) with a chloroform–ethanol, 14:1, system (A). Compounds IVa and IVb were isolated in 46 and 39% yield respectively. The deacylated dinucleoside Va was obtained in 64% yield by treatment of compound IVa with ammonia.

$N_{(1)}$-$N_{(1')}$-Di(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-[$N_{(3)}$-(uracilyl-5)-6-azathymine] (IVa, $C_{30}H_{35}N_5O_{18}$), mp 113-116°C (propanol-2). TLC (A): R_f 0.43. UV Spectrum (ethanol): λ_{max} 268, ε 13,480. ^{1}H NMR spectrum (DMSO-d_6, 200 MHz): 12.58 (1H, s, $N_{(3)}$-H), 8.20 (1H, s, 6'-H), 6.23 (1H, d, J_{12} = 2.62 Hz, 1-H of ribose at $N_{(1)}$), 6.02 (1H, d, J_{12} = 0.82 Hz, 1-H of ribose at $N_{(1')}$), 5.61-5.30 (4H, m, protons at $C_{(2)}$ and $C_{(3)}$ of ribofuranose), 4.36-3.97 (6H, m, protons at $C_{(5)}$ atoms), 2.09 (3H, s, 5-CH_3), 2.07-1.96 ppm (18H, m, acetate).

$N_{(1)}$,$N_{(1')}$,$N_{(3')}$-Tri(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-[$N_{(3)}$-(uracilyl-5)-6-azathymine](IVb,$C_{41}H_{49}N_5O_{25}$), mp 104-105°C (propanol-2). TLC (A): R_f 0.65. UV Spectrum (ethanol): λ_{max} 268, ε 10,710. ^{1}H NMR spectrum (DMSO-d_6, 200 MHz): 8.11 (1H, s, 6'-H), 6.34 (1H, d, J_{12} = 2.62 Hz, 1-H at $N_{(1)}$), 6.08 (1H, d, J_{12} = 1.86 Hz, 1-H at $N_{(1')}$), 5.88 (1H, d, J_{12} = 2.45 Hz, 1-H at $N_{(3')}$, 5.76-5.34 (6H, m, protons at $C_{(2)}$ and $C_{(3)}$ of ribofuranose), 4.42-3.88 (9H, m, 4-H, protons at $C_{(5)}$ atoms), 2.12 (3H, s, 5-CH_3), 2.09-1.98 ppm (27H, m, acetate).

$N_{(1)}$,$N_{(1')}$-Di(β-D-ribofuranosyl)-[$N_{(3)}$-(uracilyl-5)-6-azathymine] (Va, $C_{18}H_{23}N_5O_{12}$), mp 120-122°C. TLC (4:1 chloroform–ethanol) R_f 0.24. UV Spectrum (ethanol): λ_{max} 272, ε 11,240. ^{1}H NMR spectrum (DMSO-d_6, 200 MHz): 11.78 (1H, s, $N_{(3')}$-H), 7.72 (1H, s, 6'-H), 5.82 (1H, d, J_{12} = 2.62 Hz, 1-H at $N_{(1)}$), 5.68 (1H, d, J_{12} = 2.14 Hz, 1-H at $N_{(1')}$), 4.86-4.12 (10H, br. m, ribofuranose protons), 2.34 ppm (3H, s, 5-CH_3).

Elemental analyses for C, H and N corresponded to calculated values.

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