Notes

[Chem. Pharm. Bull. 22(5)1198—1200(1974)]

UDC 547.853.3'456.057 : 615.277.3.011.5

Synthesis of a Potential Antitumor Agent: 4-(β-D-Ribofuranosyl)-4,5,6,7-tetrahydrothiazolo[4,5-*d*]pyrimidine-5,7-dione (Thioanalog of 3-Isoxanthosine)[1]

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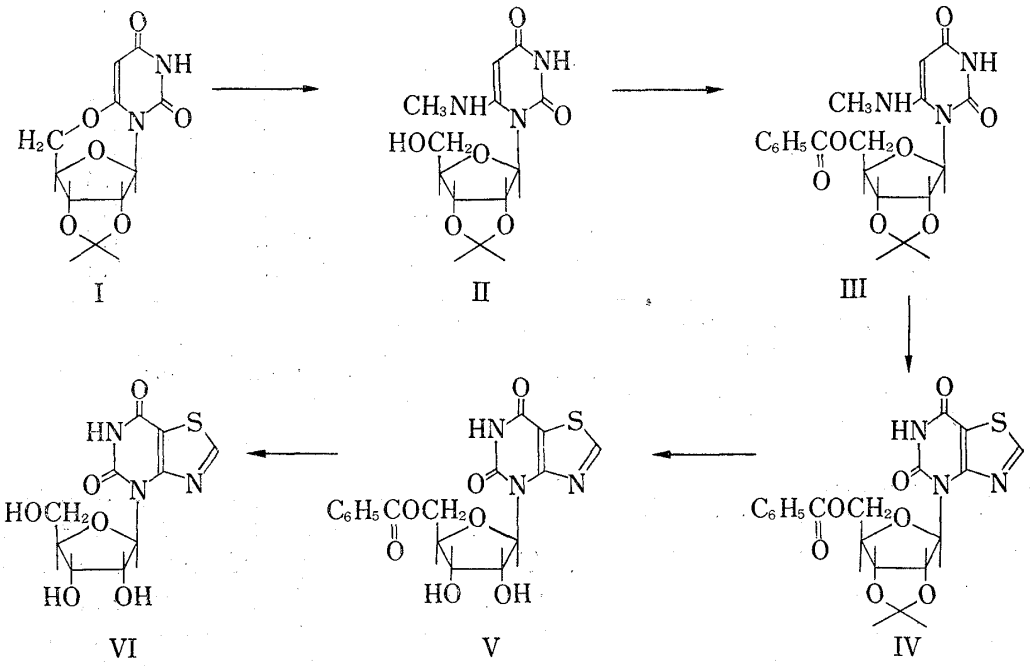
(Received August 17, 1973)

In recent years there has been an increased interest in isopurine nucleosides and nucleotides because of their potential antitumor activitities and activities in enzyme-catalyzed reactions.[3-8] We wish to report a synthesis of a 1-thioanalog of 3-isoxanthosine: 4-(β-D-ribofuranosyl)-4,5,6,7-tetrahydrothiazolo[4,5-*d*]pyrimidine-5,7-dione (VI).

The nucleoside analog was prepared by an extention of Goldman's procedure for the preparation of 4,5-dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-*d*]pyrimidine-5,7-dione from 1,3-dimethyl-6-methylaminouracil.[9] The first step in the synthesis of VI involves the conversion of 2',3'-0-isopropylidene-O^6,5'-cyclouridine (I) to 2',3'-0-isopropylidene-6-methylaminouridine



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9) I.M. Goldman, *J. Org. Chem.*, **34**, 3285 (1969).

(II); compound (I) was treated according to Lipkin and coworkers' procedure[10] with methylamine at 50—60° in a sealed tube to give II, mp 137—139° in a yield of 82%. The structure was confirmed by comparison of the ultraviolet absorption (UV) spectra with those of 6-aminouridine[10] and by its combustion values. Nuclear magnetic resonance (NMR) data were also consistent with the structure assigned. Benzoylation of the compound (II) by a conventional procedure afforded 2′,3′-0-isopropylidene-5′-0-benzoyl-6-methylaminouridine (III), mp 190—192° in an yield of 64.6%, which in turn was treated with freshly distilled thionyl chloride in the presence of pyridine according to Goldman's procedure.[9] After purification by a silica gel column chromatography, compound (IV), mp 158—160° was obtained in a yield of 42.5%, along with 10% yield of the corresponding deacetonized product (V). The latter was presumably formed during the work-up. The structure assignment of each product (V and VI) rests upon their combustion values and UV spectra. Treatment of IV with 85% aq. acetic acid afforded 5′-0-benzoyl 1-thioisoxanthosine (V), which in turn was deblocked with methanolic sodium methoxide to afford 1-thioisoxanthosine (VI). Recrystallization from methanol afforded the analytical sample, mp 207—210° in a yield of 57%. The structure assignment is consistent with its combustion values and spectral data UV, NMR and infrared (IR) spectra. The ultraviolet absorption maximum appeared at 293 nm (ε 10000). The activity of VI will be reported separately.

Experimental[11]

2′,3′-O-Isopropylidene-6-methylaminouridine (II)——A solution of 2′,3′-0-isopropylidene-5′,6-cyclouridine (I)[12] (11 g, 39 mmoles) in dry methylamine (100 ml) was heated at 50—60° for 24 hr in a sealed tube. After cooling the mixture was dissolved in $CHCl_3$ (50 ml). The resulting solution was concentrated to dryness. The residue was again dissolved in $CHCl_3$ (20 ml). The solution was applied to a column (silica gel, 200 g). The column was washed with $CHCl_3$–EtOH (14: 1 v/v). Fractions having *Rf* 0.4 in TLC (silica gel, $CHCl_3$–EtOH 3: 2) were collected. After concentration the residue (10 g, 81.9%) was recrystallized from EtOH–AcOEt to afford an analytical sample: mp 137—139° (hygroscopic). UV λ_{max}^{EtOH} nm 271; λ_{min}^{EtOH} nm 241. NMR (DMSO-d_6) δ ppm: 1.38 (d, 6H, $C(CH_3)_2$); 2.61 (d, 3H, N-CH_3); 3.63 (s, 2H, 5′-H); 4.05 (d, 1H, 4′-H); 4.50 (s, 1H, 5-H); 4.78 (d, 1H, 3′-H); 5.02 (d, 1H, 2′-H); 5.56 (broad, 1H, NH(CH_3)); 6.22 (d, 1H, 1′-H); 6.99 (broad, 1H, 5′-OH). On addition of D_2O, doublet at 2.61 ppm was collapsed into a singlet and signals at 5.56 and 6.99 ppm disappeared. IR (KBr, cm^{-1}): 3300 (NH); 1725 (C=O). *Anal.* Calcd. for $C_{13}H_{19}O_6N_3$: C, 49.08; H, 5.98; N, 13.22. Found: C. 49.21; H, 6.04; N, 13.31.

2′,3′-O-Isopropylidene-5′-O-benzoyl-6-methylaminouridine (III)——A solution of II (2 g, 6.38 mmoles) in pyridine (30 ml) was treated with benzoyl chloride (2.2 ml, 18.8 mmoles) at 67—70° for 60 hr. The solvent was evaporated to dryness. The residue was purified by a silica gel chromatography (silica gel, *ca.* 30 g, solvent system, $CHCl_3$–EtOH 24: 1). Fractions containing III were collected and concentrated to dryness. Crystallization of the residue from ethyl acetate afforded an analytical sample (1.72 g, 64.6%), mp 190—192°. UV λ_{max}^{EtOH} nm: 269; λ_{min}^{EtOH} nm: 230; λ_{max}^{pH2} nm: 270; λ_{min}^{pH2} nm: 247; λ_{max}^{pH10} nm: 272; λ_{min}^{pH10} nm: 249. NMR ($CDCl_3$) δ ppm: 1.75 (d, 6H, C $(CH_3)_2$; 2.61 (d, 3H, N-CH_3); 4.52 (s, 2H, 5′-H); 4.77 (m, 1H, NH); 6.13 (d, 1H, 1′-H); 7.5—8.0 (m, 5H, phenyl); 9.44 (s, 1H, NH in imide). On addition of D_2O a signal at 9.44 disappeared. IR (KBr): 3350 cm^{-1} (NH), 1740 (C=O), 1720 (C=O), 1640, 1595, 1547 (aromatic C=C). *Anal.* Calcd for $C_{20}H_{23}O_7N_3$: C, 57.55; H, 5.55; N, 10.07. Found: C, 57.27; H, 5.45; N, 9.89.

4-(2,3-O-Isopropylidene-5-O-benzoyl-β-D-ribofuranosyl)4,5,6,7-tetrahydrothiazolo[4,5-*d*]pyrimidine-5,7-dione (IV)——A solution of III (538 mg, 1.29 mmoles) in dry pyridine (2 ml) was refluxed with freshly distilled $SOCl_2$ (20 ml) for 45 min. Excess $SOCl_2$ and the solvent were removed *in vacuo*. Remaining $SOCl_2$ was completely destroyed with EtOH (5 ml). The solution was concentrated to dryness. The residue was dissolved in $CHCl_3$ (30 ml) and applied to a column (silica gel, *ca.* 100 g). The column was washed with $CHCl_3$–EtOH (24: 1). Fractions having *Rf* 0.50 in TLC (silica gel, $CHCl_3$–EtOH 4: 5) were pooled. On evaporation

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11) Melting points were taken in a capillary apparatus and uncorrected. UV spectra were determined in a Hitachi Spectrophotometer type 3T, and IR in KBr mull. Chemical shifts were reported in parts per million downfield from tetramethylsilane as internal standard. Unless otherwise specified, the solvent was removed under reduced pressure with a rotating evaporator. Screening of the antitumor activity of VI has been done by Drs K. Kuretani and A. Hoshi in the National Cancer Institute.
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compound (IV) was obtained in an yield of 55.2% (317 mg). Recrystallization from MeOH afforded an analytical sample (244 mg, 42.5%), mp 122—124°. UV λ_{max}^{EtOH} nm: 230, 294. *Anal.* Calcd. for $C_{20}H_{19}O_7N_3S$: C, 53.93;H, 4.30; N, 9.44; S, 7.18. Found: C, 53.69; H, 4.24; N, 9.31; S, 6.92.

The column was then washed with $CHCl_3$–EtOH (10: 1). Fractions having *Rf* 0.32 (TLC in the above solvent system) were pooled. Evaporation of the solvent left V (44 mg, 10%), mp 122—124° (recrystallized from EtOH). *Anal.* Calcd. for $C_{17}H_{15}N_3S \cdot 1/4H_2O$: C, 49.82; H, 3.66; N, 10.25. Found: C, 49.90; H, 3.63; N, 10.31.

4-(5-O-Benzoyl-β-D-ribofuranosyl)-4,5,6,7-tetrahydrothiazolo[4,5-*d*]pyrimidine-5,7-dione (V)——A solution of IV (54 mg, 0.12 mmole) in AcOH (2 ml), H_2O (8 ml) and dioxane (4 ml) was refluxed for 1.5 hr. After cooling the solution was concentrated to dryness. The residue was triturated with a mixture of methanol and ethyl ether and collected by filtration. Yield, 32 mg (65.3%). Recrystallization from MeOH afforded an analytical sample, mp 122—124°. UV λ_{max}^{EtOH} nm: 230, 294. *Anal.* Calcd. for $C_{17}H_{15}O_7N_3S \cdot 1/4H_2O$: C, 49.82; H, 3.66; N, 10.25. Found: C, 50.01; H, 3.72; N, 10.39.

4-(β-D-Ribofuranosyl)-4,5,6,7-tetrahydrothiazolo[4,5-*d*]pyrimidine-4,5-dione (VI)——To a solution of V (101 mg, 0.25 mmole) in absolute EtOH (20 ml) was added 0.1N methanolic sodium methoxide (2.5 ml). The solution was refluxed for 1 hr and then neutralized with a resin (Dowex 50W, H^+ form) and concentrated to dryness. The residue was washed twice with $CHCl_3$. Recrystallization from MeOH afforded 43 mg (57%) of VI, mp 207—210°. UV $\lambda_{max}^{H_2O}$ nm (ε): 293 (1050); 293 (pH 2); 298 (pH 10); $\lambda_{max}^{H_2O}$ nm: 257; 257 (pH 2); 273 (pH 10). NMR (D_2O) δ ppm: 4.0 (s, 2H, 5′-H); 4.57 (d, 1H, 4′-H); 4.90 (d, 1H, 3′-H); 5.11 (d, 1H, 2′-H); 6.60 (d, 1H, 1′-H); 9.50 (s, 1H, 2-H). IR (KBR, cm^{-1}): 1550, 1138, 1081, 1045. *Anal.* Calcd. for $C_{10}H_{11}O_6N_3S$: C, 39.87; H, 3.68; N, 13.95; S, 10.63. Found: C, 39.73; H, 3.58; N, 13.67; S, 10.53.

Acknowledgement This work was supported in part by the Grant-in-Aid from The Ministry of Education. Our thanks are due to Miss H. Kakizaki who has performed the elemental analyses.

[Chem. Pharm. Bull. 22(5)1200—1202(1974)]

UDC 547.857.4.057 : 547.857.5.04

Facile Syntheses of Xanthines from Uric Acids

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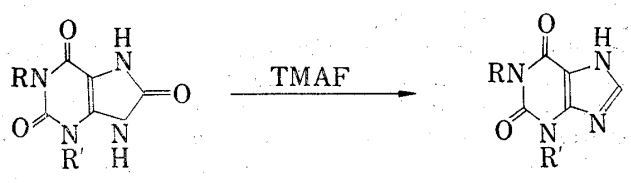
(Received August 27, 1973)

Direct conversion of uric acid into xanthine and related reaction have been realized by Bredereck[2] by means of heating with formamide at elevated temperature. It has now been found that the same conversion can be effected by heating with the distillable liquid formate composed of formic acid and trialkylamine. When uric acid (Ia) was heated at 175—180° along with the formate, trimethylammoniun formate (TMAF),[3] bp 91—93° (18 mmHg), which may be given by $5HCO_2H \cdot 2NMe_3$, the reaction proceeded with emission of carbon dioxide to give xanthine (IIa) in 96% yield. By the same manner 3-methylxanthine (IIb) from 3-methyluric acid (Ib) and theophylline (IIc) from 1,3-dimethyluric acid (Ic) were also realized in 91% and 97% yield, respectively. On control experiment TMAF was shown to



Ia—c
a : R=R′=H
b : R=H; R′=CH_3
c : R=R′=CH_3

IIa—c

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