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Note

A two-step, regioselective synthesis of 3-hypoxanthosine and 3-hypothioxanthosine derivatives

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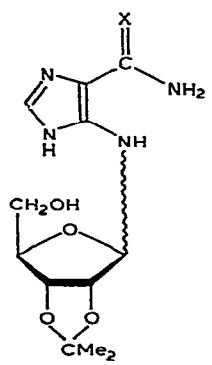
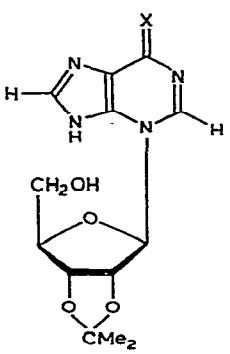
Although the 3-D-ribofuranosylpurines have interesting biological activities[1–7], their description is not well-documented, because of their relative instability[8,9] compared to that of the 7- or 9-isomers.

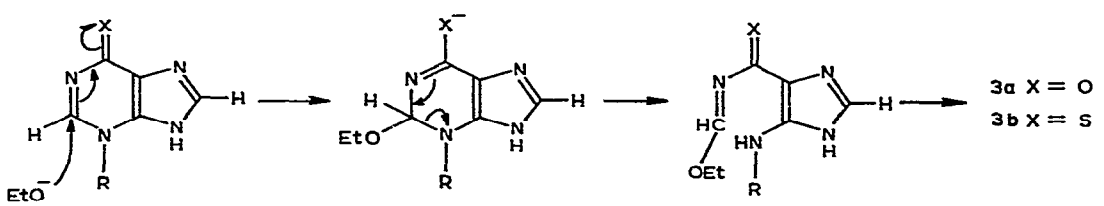
Generally, by using direct-coupling techniques, the 3-D-ribofuranosylpurines can be obtained as isomeric mixtures with the corresponding 9-isomer[10–14]. However, the presence of a bulky halogen atom at position 8 of the purine ring causes pre-



3a X = O
3b X = S



4a X = O
4b X = S

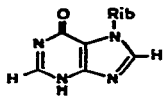
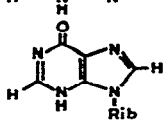
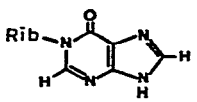
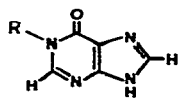
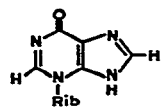
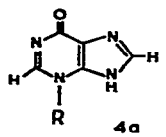
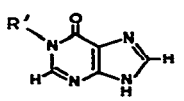
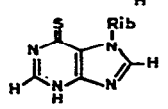
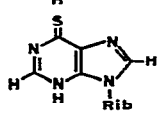
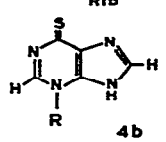


5 6 7

ponderance of N-3 substitution, but subsequent elimination of the halogen atom is not straightforward[15,16]. Furthermore, a five-step synthesis of 3-isoxanthosine from a D-ribofuranosylpyrimidine followed by ring closure has been reported[17].

TABLE I

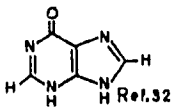
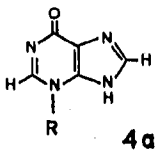
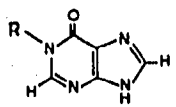
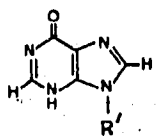
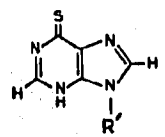
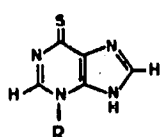
U.V. DATA: λ_{max} (ε)

	Ref.	*pH 1*	*pH 6.7*	*pH 7*	*pH 9*	*pH 11*	*pH 13*	*MeOH*
	25	252 (9230)		257 (8420)		263 (8830)		
	26	249 (11600)		248 (12100)		253 (13000)		
	27	249 (9580)		251 (8550)		261 (8530)		
	28	249 (9800)		250 (10000)			261) (10600)	
	16	254 (10950)		265 (13200)		270 (10900)		
 4a		254 (11200)		263 (12300)		276 (11000)		
	28	320 (18900)		321 (23000)		321 (20800)		
	29	330 (18700)				317 (20400)		332 (16000)
	30	322 (22500)	320 (21500)				310 (22100)	
 4b		322 (17900)		341 (22000)	339 (16000)			

[a]R = 2,3-*O*-Isopropylidene-β-D-ribofuranosyl. R′ = 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl.

TABLE II

^{13}C-N.M.R. DATA[a]

Compound[b]	*C-2*	*C-4*	*C-5*	*C-6*	*C-8*	*C-1′*	*C-2′*	*C-3′*	*C-4′*	*C-5′*	O>C<O	*CH*$_3$
 Ref.32	150.20	155.50	118.00	158.90	144.80							
 4a	140.31	146.45	114.61	161.77	144.60	93.83	86.65	83.10	80.95	61.45	113.14	27.01 25.11
	141.13	154.16	112.90	145.38	145.38	90.95	87.44	84.56	80.76	61.25	112.89	27.01 25.16
 Ref.32	149.20	146.95	125.30	157.65	139.90	88.75	71.20	75.15	86.60	62.25		
 Ref.32	146.10	144.70	136.30	176.70	141.90	88.45	70.85	75.10	86.40	61.95		
 4b	139.09	140.59	128.45	184.74	143.74	94.41	87.73	83.93	80.65	61.25	112.89	26.87 25.01

[a] Measured in (CD$_3$)$_2$SO (internal Me$_4$Si). [b] R = 2,3-*O*-isopropylidene-β-D-ribofuranosyl, R′ = β-D-ribofuranosyl.

We now describe a short, general, regioselective synthesis in the 3-D-ribofuranosylpurine series, starting from the commercially available 5-amino-4-carbamoylimidazole AICA (**1a**) or the corresponding 5-amino-4-thiocarbamoylimidazole[18–20] (**1b**).

Condensation[21] of **1a** or **1b** with 2,3-*O*-isopropylidene-D-ribofuranose[22] (**2**) gave the glycosylamines **3a** (50%) or **3b** (76%). Treatment of **3a** or **3b** in boiling ethanol with ethyl formate and sodium ethoxide afforded **4a** (50%) or **4b** (21%) after chromatography. It was observed (by t.l.c.) that, during the cyclisation step, **3a** or **3b** was always present even after prolonged boiling, presumably because of a reverse reaction (**5**→**6**→**7**), since **4a** or **4b**, when treated with sodium ethoxide in boiling ethanol, gave some **3a** or **3b**.

Mass spectrometry of **4a** and **4b** showed characteristic fragmentation processes of hypoxanthine derivatives[23]. The downfield chemical-shift of the imidazole proton from δ 7.40 for H-2 in **3a** or **3b** to δ 8.25 or 8.17 for H-8 of **4a** or **4b** confirm the ring-closure process[24]. The u.v. data in Table I show that **4a** is a 3-hypoxanthosine derivative. Since no such reference compound was available for **4b**, ^{13}C-n.m.r. spectroscopy was used to confirm the site of ribosylation. Ribosylation at N-7 or N-9 of a purine ring produces[31] a downfield shift of the carbon signal in comparison with those of the corresponding aglycon. Table II illustrates such an effect for C-2 of **4a** and 1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine[28], as compared with hypoxanthine. The downfield shift of 7 p.p.m. for C-2 of 6-thioinosine, compared with **4b**, is consistent with a 3-D-ribofuranosyl-6-thiohypoxanthine.

The anomeric configuration of **4a** and **4b** was determined on the basis of known[33] criteria. Thus the chemical-shift difference ($\Delta\delta$ 0.15 p.p.m.) for the 2,3-*O*-isopropylidene methyl groups of a nucleoside is typical of a β anomer. Since $\Delta\delta$ is 0.24 p.p.m. for **4a** and **4b**, these compounds are 3-hypoxanthosine and 3-hypothioxanthosine derivatives, respectively.

EXPERIMENTAL

General methods. — Melting points were determined on a Gallenkamp apparatus and are uncorrected. T.l.c. was performed on aluminium foils precoated with silica gel F-254 (Merck) with detection by u.v. light or charring with sulphuric acid. Column chromatography was performed with silica gel (70–230 mesh ASTM, Merck).

Optical rotations were determined with a Perkin–Elmer 241 MC polarimeter, and u.v. spectra with an Optica model 10 spectrometer. ^{1}H-N.m.r. spectra were recorded with Varian T60 or HA-100 spectrometers, and ^{13}C-n.m.r. spectra with Bruker WP-80 or Jeol PS-100 spectrometers on solutions in Me_2SO-d_6 (internal Me_4Si); chemical shifts are expressed on the δ scale. Mass spectra were recorded on a Jeol JMS D100 spectrometer by the direct-insertion procedure.

Analyses were performed by the "Service Central de Micro-Analyse du C.N.R.S.", division de Montpellier.

4-Carbamoyl-5-(2,3-O-isopropylidene-D-ribofuranosylamino)imidazole (**3a**). — A solution of 5-amino-4-carbamoylimidazole (**1a**; 4.21 g, 0.033 mol) in anhydrous ethanol (30 ml) containing 2,3-*O*-isopropylidene-D-ribofuranose (**2**) (6.36 g, 0.033 mol) and Sikkon Blue Fluka (1 g) was boiled under reflux for 30 h and then decolorised with charcoal, filtered through Celite, and concentrated *in vacuo*. The residue was purified by column chromatography (chloroform–methanol, 9:1) and crystallised from water to afford **3a** (4.95 g, 50%), m.p. 146–148°, $[\alpha]_D^{20}$ −6° (*c* 1, methyl sulphoxide). P.m.r. data: δ 1.30 (s, 3 H, Me), 1.47 (s 3 H, Me), 3.30–3.50 (m, 2 H, H-5′5″), 3.70–3.94 (m, 1 H, H-4′), 4.60–4.80 (m, 2 H, H-2′,3′), 5.24–5.50 and 5.68–5.90 (m, H-1′, anomers), and 7.40 (s, 1 H, H-2). ^{13}C-N.m.r. data: α anomer, δ 24.85 (Me), 25.98 (Me), 62.72 (C-5′), 78.96 (C-4′), 80.97 (C-3′), 81.56 (C-2′), 84.61 (C-1′), 111.83 (CMe_2), 131.49 (C-2,5), 147.05 (C-4), and 164.30 (-C=O); β anomer, δ 24.94 (Me), 26.71 (Me), 62.08 (C-5′), 78.96 (C-4′), 81.56 (C-3′), 84.24 (C-2′), 90.62 (C-1′), 112.15 (CMe_2), 131.49 (C-2,5), 146.46 (C-4), and 164.62 (-C=O).

Anal. Calc. for $C_{12}H_{18}N_4O_5 \cdot H_2O$: C, 45.67; H, 6.37; N, 17.71. Found: C, 45.77; H, 6.38; N, 17.72.

5-(2,3-O-Isopropylidene-D-ribofuranosylamino)-4-thiocarbamoylimidazole (**3b**). — A solution of 5-amino-4-thiocarbamoylimidazole[18–20] (**1b**; 1.4 g, 0.01 mol) and 2,3-*O*-isopropylidene-D-ribofuranose (**2**; 1.4 g, 0.013 mol) in anhydrous ethanol (10 ml) was boiled under reflux for 3 h and then decolorised with charcoal, filtered through Celite, and concentrated. The yellow syrup crystallised on treatment with chloroform (15 ml). Recrystallisation from water afforded **3b** (2.4 g, 76%), m.p. 189–190°, $[\alpha]_D^{20}$ −18° (*c* 1, methyl sulphoxide). P.m.r. data: δ 1.33 (s, 3 H, Me), 1.50 (s, 3 H, Me), 3.30–3.60 (m, 2 H, H-5′5″), 3.80–4.00 (m, 1 H, H-4′), 4.60–4.90 (m, 2 H, H-2′,3′), 5.34–5.60 and 5.76–6.06 (m, 1 H, H-1′), and 7.40 (s, 1 H, H-2).

Anal. Calc. for $C_{12}H_{18}N_4O_4S$: C, 45.84; H, 5.77; S, 10.19. Found: C, 45.54; H, 5.44; S, 10.39.

3-(2,3-O-Isopropylidene-β-D-ribofuranosyl)hypoxanthine (**4a**). — To a solution of dry **3a** (5 g, 0.017 mol) in 0.7M ethanolic sodium ethoxide (110 ml) was added freshly purified ethyl formate (5.41 ml). The solution was boiled under reflux for 3 h and then decolorised with charcoal, filtered through Celite, and concentrated. The oily residue was purified by column chromatography (chloroform–methanol, 9.7:0.3) and crystallised from methanol to give **4a** (3 g, 57%), m.p. 133–135°, $[\alpha]_D^{20}$ −37° (*c* 1, water). P.m.r. data: δ 1.31 (s, 3 H, Me), 1.55 (s, 3 H, Me), 3.46–3.82 (m, 2 H, H-5′,5″), 4.16–4.34 (m, 1 H, H-4′), 4.98 (dd, 1 H, $J_{3',4'}$ 3 Hz, H-3′), 5.30 (dd, 1 H, $J_{2',3'}$ 6 Hz, H-2′), 6.18 (d, 1 H, $J_{1',2'}$ 2.9 Hz, H-1′), 8.25 (s, 1 H, H-8), and 8.60 (s, 1 H, H-2). Mass spectrum: *m/e* 308 (M^+, 18%), 293 (M^+ −Me, 32), 277 (M^+ −CH_2OH, 10), 250 (M^+ −Me−COMe, 14), 219 (M^+ −Me COMe−CH_2OH, 60), 173 (sugar $^+$, 40), 137 (base B^+ + 2 H, 90), 136 (B^+ + H, 100), 135 (B^+, 25), 109 (B^+ − HCN, 60), 108 (B^+ −CO, 40), 81 (B^+ − HCN−CO or B^+ −CO−HCN, 60), and 54 (B^+ −HCN−CO−HCN, 50).

Anal. Calc. for $C_{13}H_{16}N_4O_5$: C, 50.64; H, 5.23; N, 18.19. Found: C, 50.49; H, 5.18; N, 18.20.

3-(2,3-O-Isopropylidene-β-D-ribofuranosyl)-6-thiohypoxanthine (**4b**). — A solution of **3b** (1.5 g, 0.0048 mol) in ethanolic sodium ethoxide (30 ml, 0.7M) containing freshly purified ethyl formate (1.7 ml) was boiled under reflux for 3 h, and then neutralized with M HCl, treated with charcoal, filtered through Celite, and concentrated *in vacuo*. The residue was purified by column chromatography (chloroform–methanol, 8.5:1.5) and crystallised from acetone to afford **4b** (0.325 g, 21%), m.p. 205–206°, $[\alpha]_D^{20}$ −11° (*c* 1, methanol). P.m.r. data: δ 1.32 (s, 3 H, Me), 1.56 (s, 3 H, Me), 3.45–3.84 (m, 2 H, H-5′,5″), 4.16–4.42 (m, 1 H, H-4′), 4.96 (dd, 1 H, $J_{3',4'}$ 3 Hz, H-3′), 5.31 (dd, 1 H, $J_{2',3'}$ 6 Hz, H-2′), 6.25 (d, 1 H, $J_{1',2'}$ 2.5 Hz, H-1′), 8.38 (s, 1 H, H-8), and 8.67 (s, 1 H, H-2). Mass spectrum: *m/e* 324 (M^+, 14%), 309 (M^+ −Me, 10), 293 (M^+ −CH_2OH, 8), 266 (M^+ −MeCOMe, 15), 225 (M^+ −MeCOMe−CH_2OH, 20), 173 (sugar $^+$, 18), 153 (B^+ + 2 H, 32), 152 (B^+ + H, 100), 151 (B^+, 10), 125 (B^+ − HCN, 25), and 114 (B^+ −CH_2−C=S, 50).

Anal. Calc. for $C_{13}H_{16}N_4O_4S$: C, 48.14; H, 4.97; S, 9.88. Found: C, 48.17; H, 5.00; S, 9.65.

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