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Note

Unsaturated ketonucleosides of adenine and hypoxanthine

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Unsaturated ketonucleosides have significant *in vitro* and *in vivo* inhibitory activity against various types of cancer cell[1–3]. In developing structure–activity relationships, we have synthesised several unsaturated ketonucleosides and related compounds[4] and now describe the first synthesis of the unsaturated ketonucleosides of adenine and hypoxanthine in the L and D series.

Thus, α-L-rhamnopyranosyladenine[5] (**4a**) was converted into the hypoxanthine derivative **4b** by treatment with nitrous acid. Selective benzoylation[6] of **4a** and **4b** gave the dibenzoates **5a** and **5b**, respectively, and subsequent treatment with methyl sulfoxide–acetic anhydride at 100° for 10 min led to the corresponding unsaturated ketonucleosides **6a** and **6b**. Attempted oxidation of the adenine nucleosides **5a** and **9a** with Cr(VI) reagents[7–9] failed and, with methyl sulfoxide–dicyclohexylcarbodi-imide[10], an intractable mixture of by-products was formed. The procedure reported for the oxidation of a pentofuranosyladenine by a chromium reagent[11] did not give reproducible results with hexopyranosyl nucleosides. Treatment of **5a**, in the usual manner, with either pyridinium dichromate or pyridinium chlorochromate or CrO_3–pyridine resulted in the recovery of only small amounts of starting material and no oxidation products. This suggests that there may be much stronger interaction of the adenine nucleoside and the chromium species, compared to the pentofuranosyl nucleosides. Albright's reagent (Me_2SO–Ac_2O)[12] was the only suitable oxidant found so far, but it was not possible to avoid the *N*-acetylation of **6a** and **10a**. No *O*-acetylated by-products could be detected. As previously observed[4], β-elimination of benzoic acid occurred spontaneously during the oxidation process, leading exclusively to the unsaturated compounds.

Similar experiments were conducted in the D series, using 6-deoxy-D-glucose[13] as the starting material. Condensation of the tetra-acetate with bis(trimethylsilyl)-*N*-benzoyladenine led to the corresponding nucleoside **7**. The $J_{1,2}$ value of 9 Hz was consistent with the β configuration in the $^4C_1$ conformation. These findings accord with those reported by Lichtenthaler *et al.*[14] for various glucosyl nucleosides. Compound **7** had λ_{max} 280 nm characteristic of a 9-nucleoside, and was

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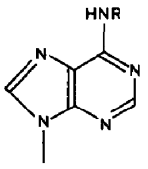
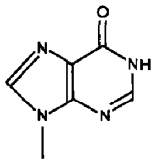
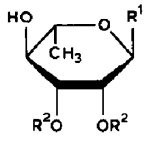


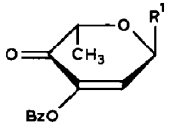
1 R = H
2 R = Bz



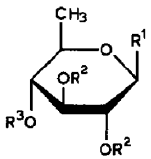
3



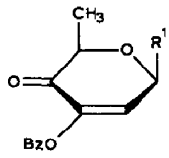
4a $R^1 = 1, R^2 = H$
4b $R^1 = 3, R^2 = H$
5a $R^1 = 1, R^2 = Bz$
5b $R^1 = 3, R^2 = Bz$



6a $R^1 = 1$
6b $R^1 = 3$



7 $R^1 = 2, R^2 = R^3 = Ac$
8a $R^1 = 1, R^2 = R^3 = H$
8b $R^1 = 3, R^2 = R^3 = H$
9a $R^1 = 1, R^2 = Bz, R^3 = H$
9b $R^1 = 3, R^2 = Bz, R^3 = H$



10a $R^1 = 1$
10b $R^1 = 3$

transformed into the unsaturated D-ketonucleosides **10a** and **10b** through the reaction sequence described above.

Preliminary results for various tumor cells indicated that the unsaturated ketonucleosides of adenine and hypoxanthine are more active than their purine nucleoside counterparts. The detailed biological activity of these compounds will be described elsewhere.

EXPERIMENTAL

General. — Reactions were monitored by t.l.c. on silica gel 60F (Merck) with ethyl acetate–ethanol (*A*, 4:1; *B*, 1:1) and dichloromethane–acetone (*C*, 6:4). ^{1}H-N.m.r. spectra (internal Me_4Si) were recorded at 60 MHz. Melting points are uncorrected. Elemental analyses were made at the "Service Central de Microanalyses du CNRS" (Vernaison, France).

9-α-L-Rhamnopyranosylhypoxanthine (**4b**). — A solution of **4a**[5] (1 g, 3.6 mmol) and sodium nitrite (0.59 g, 8.6 mmol) in water (20 mL) and acetic acid (3.7 mL) was stirred for 6 h at room temperature[15]. Disappearance of u.v. absorption at 260 nm indicated the end of the reaction. The mixture was deionised with Amberlite IR-120 (H^+) resin and concentrated, and the residue was crystallised

from acetone–ethanol to yield **4b** (0.75 g, 74%), m.p. 195° (dec.), $[\alpha]_D$ +20° (*c* 1, water), R_F 0.3 (solvent *B*). ^{1}H-N.m.r. data (Me_2SO): δ 8.20 (s, 1 H, H-2), 8.10 (s, 1 H, H-8), 7.13 (bs, 1 H, N-H), 5.87 (d, 1 H, $J_{1,2}$ 4 Hz, H-1′), 5.05 (m, 2 H, H-2′,3′), 1.32 (d, 3 H, $J_{5,6}$ 6 Hz, H-6′,6′,6′).

Anal. Calc. for $C_{11}H_{14}N_4O_5 \cdot 0.75\ H_2O$: C, 44.67; H, 5.25; N, 18.95. Found: C, 44.90; H, 5.00; N, 19.0.

6-N-Benzoyl-9-(2,3,4-tri-O-acetyl-6-deoxy-β-D-glucopyranosyl)adenine (**7**). — A solution of 1,2,3,4-tetra-*O*-acetyl-6-deoxy-α-D-glucopyranose[13] (5 g, 15 mmol) in dichloroethane (60 mL) containing bis(trimethylsilyl)-*N*-benzoyladenine[16] (1.1 equiv., 16.5 mmol) was boiled under reflux in the presence of tin(IV) chloride. After 1 h, the mixture was cooled and neutralised with saturated aqueous sodium hydrogencarbonate, and the organic phase was then washed twice with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was crystallised from ethanol to yield **7** (6.1 g, 80%), m.p. 125°, $[\alpha]_D$ +18° (*c* 1, methanol), R_F 0.7 (solvent *A*). ^{1}H-N.m.r. data ($CDCl_3$): δ 9.40 (b, 1 H, N-H), 8.82 (s, 1 H, H-2), 8.28 (s, 1 H, H-8), 8.18–7.4 (m, 5 H, Ph), 6.0 (d, 1 H, $J_{1,2}$ 9 Hz, H-1′), 5.07 (t, 1 H, $J_{3,4}$ 9 Hz, H-4′), 3.93 (dq, 1 H, $J_{4,5}$ 9, $J_{5,6}$ 6 Hz, H-5′), 2.13 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 1.78 (s, 3 H, Ac), 1.32 (d, 3 H, $J_{5,6}$ 6 Hz, H-6′,6′,6′).

Anal. Calc. for $C_{24}H_{25}N_5O_8$: C, 56.36; H, 4.89; N, 13.70. Found: C, 56.19; H, 4.92; N, 14.00.

9-(6-Deoxy-β-D-glucopyranosyl)adenine (**8a**). — To a solution of **7** (1 g, 1.96 mmol) in methanol (10 mL) was added methanolic 2M sodium methoxide (2 mL). The mixture was stirred overnight at room temperature, then neutralised with IR-120 (H^+) resin, and concentrated to give **8a** (0.33 g, 60%), m.p. 270° (dec.), $[\alpha]_D$ +55° (*c* 0.1, methanol). ^{1}H-N.m.r. data (Me_2SO): δ 8.28 (s, 1 H, H-2), 8.17 (s, 1 H, H-8), 7.23 (bs, 2 H, NH_2), 5.92 (d, 1 H, $J_{1,2}$ 7 Hz, H-1′), 5.18 (b, 3 H, 3 OH), 4.60 (m, 1 H, H-2′), 1.35 (d, 3 H, $J_{5,6}$ 6 Hz, H-6′,6′,6′).

Anal. Calc. for $C_{11}H_{15}N_5O_4$: C, 46.98; H, 5.34; N, 24.91. Found: C, 47.20; H, 5.60; N, 24.30.

9-(6-Deoxy-β-D-glucopyranosyl)hypoxanthine (**8b**). — Deamination of **8a**, as described for **4a**, gave **8b** (0.6 g, 60%), m.p. 175° (dec.), $[\alpha]_D$ +20° (*c* 1, water), R_F 0.3 (solvent *B*). ^{1}H-N.m.r. data (Me_2SO): δ 8.15 (s, 1 H, H-2), 8.05 (s, 1 H, H-8), 7.10 (bs, 1 H, N-H), 5.82 (d, 1 H, $J_{1,2}$ 7 Hz, H-1′), 5.0 (b, 3 H, 3 OH), 4.57 (m, 1 H, H-2′), 1.33 (d, 3 H, $J_{5,6}$ 7 Hz, H-6′,6′,6′).

Anal. Calc. for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 4.96; N, 19.86. Found: C, 47.00; H, 4.30; N, 20.20.

9-(2,3-Di-O-benzoyl-α-L-rhamnopyranosyl)adenine (**5a**). — To a solution of **4a** in dry pyridine (100 mL) at −20° was added benzoyl chloride (3.5 mL, 2.1 equiv.), and the mixture was kept at −20° for 8 h. After the usual work-up, crystallisation from dichloromethane gave **5a** (5.2 g, 75%), m.p. 280°, $[\alpha]_D$ −30° (*c* 0.1, methanol), R_F 0.63 (solvent *B*). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.42–7.05 (m, 12 H, H-2,8 and 2 Ph), 7.0 (bs, 2 H, NH_2), 6.58 (m, 1 H, H-2′), 6.37 (d, 1 H, $J_{1,2}$ 6 Hz, H-1′), 5.88 (m, 1 H, H-3′), 5.62 (d, 1 H, OH), 4.35–3.78 (m, 2 H, H-4′,5′), 1.53 (d, 3 H, $J_{5,6}$ 5 Hz, H-6′,6′,6′).

Anal. Calc. for $C_{25}H_{23}N_5O_6$: C, 61.35; H, 4.70; N, 14.31. Found: C, 61.93; H, 4.27; N, 14.82.

9-(2,3-Di-O-benzoyl-α-L-rhamnopyranosyl)hypoxanthine (**5b**). — Using the procedure for the benzoylation of **4a, 4b** was converted into **5b** (68%), m.p. 190°, $[\alpha]_D$ +15° (*c* 0.1, methanol), R_F 0.64 (solvent *B*). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.95 (s, 1 H, H-2), 7.73 (s, 1 H, H-8), 7.77–6.93 (m, 10 H, 2 Ph), 6.27 (m, 1 H, H-2′), 6.03 (d, 1 H, $J_{1,2}$ 4 Hz, H-1′), 5.57 (m, 1 H, H-3′), 5.35 (d, 1 H, OH), 3.80 (m, 2 H, H-4′,5′), 1.50 (d, 3 H, $J_{5,6}$ 6 Hz, H-6′,6′,6′).

Anal. Calc. for $C_{25}H_{22}N_4O_7$: C, 61.22; H, 4.49; N, 11.43. Found: C, 60.95; H, 4.83; N, 10.89.

9-(2,3-Di-O-benzoyl-6-deoxy-β-D-glucopyranosyl)adenine (**9a**). — Using the procedure for the benzoylation of **4a, 8a** was converted into **9a** (72%), m.p. 210–212°, $[\alpha]_D$ +35° (*c* 0.1, methanol), R_F 0.66 (solvent *B*). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.3 (s, 1 H, H-2), 8.18 (s, 1 H, H-8), 8.05–7.22 (m, 10 H, 2 Ph), 6.22–5.78 (m, 3 H, H-1′,2′,3′), 4.9 (dd, 1 H, $J_{3,4}$ 8 Hz, H-4′), 3.75 (m, 1 H, H-5′), 1.53 (d, 3 H, $J_{5,6}$ 6 Hz, H-6′,6′,6′).

Anal. Calc. for $C_{25}H_{23}N_5O_6$: C, 61.35; H, 4.70; N, 14.31. Found: C, 61.39; H, 4.82; N, 14.04.

9-(2,3-Di-O-benzoyl-6-deoxy-β-D-glucopyranosyl)hypoxanthine (**9b**). — Using the procedure described for the deamination of **4a, 9a** was converted into **9b** (65%), m.p. 205–208°, $[\alpha]_D$ +55° (*c* 0.1, methanol), R_F 0.7 (solvent *B*). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.17 (s, 1 H, H-2), 8.03 (s, 1 H, H-8), 7.93–7.02 (m, 10 H, 2 Ph), 6.08–5.75 (m, 3 H, H-1′,2′,3′), 4.83 (m, 1 H, H-4′), 4.02 (m, 1 H, H-5′), 1.55 (d, 3 H, $J_{5,6}$ 6 Hz, H-6′,6′,6′).

Anal. Calc. for $C_{25}H_{22}N_4O_7$: C, 61.22; H, 4.49; N, 11.43. Found: C, 61.32; H, 4.05; N, 11.80.

6-Acetamido-9-(3-O-benzoyl-6-deoxy-α-L-glycero-hex-2-enopyranosyl-4-ulose)adenine (**6a**). — To a solution of **5a** (1 g, 2 mmol) in methyl sulfoxide (10 mL) was added acetic anhydride (5 mL). The solution was heated at 100° for 10 min, then diluted with ethyl acetate, and poured into ice and water. The organic layer was washed with saturated aqueous sodium hydrogencarbonate, dried ($MgSO_4$), and concentrated. The residue was crystallised from dichloromethane to yield **6a** (0.5 g, 60%), m.p. 218°, $[\alpha]_D$ −13° (*c* 0.1, methanol), R_F 0.4 (solvent *C*). ^{1}H-N.m.r. data ($CDCl_3$): δ 9.50 (bs, 1 H, NH), 8.78 (s, 1 H, H-2), 8.5 (s, 1 H, H-8), 8.28–7.33 (m, 5 H, Ph), 7.07 (d, 1 H, $J_{1,2}$ 4 Hz, H-1′*), 6.95 (d, 1 H, H-2′*), 4.58 (q, 1 H, $J_{5,6}$ 7 Hz, H-5′), 1.47 (d, 3 H, H-6′,6′,6′).

Anal. Calc. for $C_{20}H_{17}N_5O_5 \cdot 0.25\ H_2O$: C, 58.32; H, 4.25; N, 17.01. Found: C, 58.34; H, 4.20; N, 16.92.

9-(3-O-Benzoyl-6-deoxy-α-L-glycero-hex-2-enopyranosyl-4-ulose)hypoxanthine (**6b**). — Treatment of **5b**, as described above for **5a**, gave **6b** (63%), m.p. 177–179° $[\alpha]_D$ +35° (*c* 0.1, methanol), R_F 0.43 (solvent *C*). ^{1}H-N.m.r. data

*These assignments may be interchanged.

($CDCl_3$):δ 8.50–7.37 (m, 8 H, NH, H-2,8, and Ph), 6.98 (m, 2 H, H-1′,2′), 4.58 (m, 1 H, H-5′), 1.48 (d, 3 H, $J_{5,6}$ 6 Hz, H-6′,6′,6′).

Anal. Calc. for $C_{18}H_{15}N_4O_5$: C, 59.02; H, 3.83; N, 15.30. Found: C, 58.85; H, 4.00; N, 15.39.

*6-Acetamido-9-(3-O-benzoyl-6-deoxy-β-*D*-glycero-hex-2-enopyranosyl-4-ulose)adenine* (**10a**). — Treatment of **9a**, as described above for **6a**, gave **10a** (60%), m.p. 210–212°, $[\alpha]_D$ +5° (*c* 0.1, methanol), R_F 0.44 (solvent *C*). ^{1}H-N.m.r. data ($CDCl_3$): δ 9.27 (bs, 1 H, NH), 8.75 (s, 1 H, H-2), 8.42 (s, 1 H, H-8), 8.28–7.38 (m, 5 H, Ph), 7.13 (d, 1 H, $J_{1,2}$ 2 Hz, H-1′*), 6.97 (d, 1 H, H-2′*), 4.67 (q, 1 H, $J_{5,6}$ 6 Hz, H-5′), 1.52 (d, 3 H, H-6′,6′,6′).

Anal. Calc. for $C_{20}H_{17}N_5O_5 \cdot 0.3\ H_2O$: C, 58.20; H, 4.27; N, 16.97. Found: C, 58.19; H, 4.26; N, 16.97.

*9-(3-O-Benzoyl-6-deoxy-β-*D*-glycero-hex-2-enopyranosyl-4-ulose)hypoxanthine* (**10b**). — Treatment of **9b**, as described above for **6a**, gave **10b** (65%), m.p. 178–180°, $[\alpha]_D$ +17° (*c* 0.1, methanol), R_F 0.48 (solvent *C*). ^{1}H-N.m.r. data ($CDCl_3$): δ 9.13 (bs, 1 H, NH), 8.62 (s, 1 H, H-2), 8.28 (s, 1 H, H-8), 8.17–7.13 (m, 5 H, Ph), 7.03 (d, 1 H, $J_{1,2}$ 2 Hz, H-1′*), 6.87 (d, 1 H, H-2′*), 4.78 (q, 1 H, $J_{5,6}$ 6 Hz, H-5′), 1.52 (d, 3 H, H-6′,6′,6′).

Anal. Calc. for $C_{18}H_{15}N_4O_5$: C, 59.02; H, 3.83; N, 15.30. Found: C, 58.85; H, 4.10; N, 15.26.

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