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Note

N.m.r. data on ketohexose nucleosides

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The biological importance of ketohexose nucleosides has been emphasized in the past decade[1–4] and a relationship between the structure and the cytotoxic activity has been observed for several cell lines[3], which suggests that the presence of C=C–C=O or –C–C–C=O in the sugar moiety is indispensable. On the other
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hand, the activity appears to be independent of the anomeric configuration, the axial or equatorial position of the heterocyclic base, and the L or D configuration of the sugar. The mechanism of action of these compounds is still unclear, although they are known to inhibit DNA, RNA, and protein synthesis[5] and to react with sulfhydryl compounds[6]. Moreover, the absence of a genotoxic effect[4] makes these compounds of particular interest and indicates that they act by a mechanism that is probably different from that associated with alkylating or intercalating antitumor drugs.

We now report ^{13}C-n.m.r. data on various ketohexose and unsaturated ketohexose nucleosides together with ^{1}H-n.m.r. data which supplement earlier studies (see Tables I and II).

A keto group in a sugar moiety, as in 7-(6-deoxy-3,4-*O*-isopropylidene-β-L-*lyxo*-hexopyranosyl-2-ulose)theophylline[7] (**3**) and in 1-(6-deoxy-3,4-*O*-isopropylidene-β-L-*lyxo*-hexopyranosyl-2-ulose)thymine[8] (**4**), deshields the neighboring protons. Moreover, the ^{1}H-n.m.r. data for the precursors 7-(6-deoxy-3,4-*O*-isopropylidene-β-L-galactopyranosyl)theophylline[7] (**1**) and 1-(6-deoxy-3,4-*O*-isopropylidene-β-L-galactopyranosyl)theophylline[8] (**2**) indicate[9–11] a conformation close to $^{1}S_{3}$, caused by the dioxolane ring which takes up a $^{3}T_{4}$ conformation[11]. Oxidation of HO-2′ in **1** or **2** affects the 1,3-dioxolane ring so that $J_{4',5'}$ becomes <0.5 Hz. On the other hand, repulsion between the O-2 of the thymine moiety and the carbonyl oxygen of the sugar moiety causes distortions as shown by the smaller value of $J_{3',4'}$. Hence, the conformations of **3** and **4** are close to $^{3}S_{1}$. As expected, C-2′ in **3** and **4** is markedly deshielded (110–120 p.p.m.) but, whereas H-1′ is

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TABLE I

N.M.R. DATA[a] FOR SATURATED KETOHEXOSE NUCLEOSIDES AND THE PARENT NUCLEOSIDES

^{1}H-N.m.r. data

	H-1'	$J_{1',2'}$	*H-2'*	$J_{2',3'}$	H-3'	$J_{3',4'}$	H-4'	$J_{4',5'}$	H-5'	$J_{5',6'a}$	$J_{5',6'c}$	*H-6'*
5[b]	6.75						6.72	3.9	5.05		6.7	1.51
6[b]	6.80						6.57	1.3	5.13		6.8	1.53
7[b]	6.63				6.28	10.3	7.09	0	4.63		6.6	1.49
8[b]	6.61						7.50	3.0	4.76		7.0	1.59
10[c]	6.8	1.6	7.33						4.73	5.3	2.6	4.53
11[b]	6.96	1.7	7.40						4.65	4.6	4.0	4.09
12[b]	6.92	1.5	7.35						4.62		5.8	1.51
13[b]	7.05	2.1	7.00	10.2	6.31				4.41		6.6	1.39

^{13}C-N.m.r. data

	C-1'	$J_{C-1',H-1'}$	*C-2'*	$J_{C-2',H-2'}$	*C-3'*	$J_{C-3',H-3'}$	*C-4'*	$J_{C-4',H-4'}$	*C-5'*	$J_{C-5',H-5'}$	*C-6'*	$J_{C-6',H-6'}$
5[b]	80.07	172	182.7		142.1		138.4	166	70.2	145	20.3	145
6[b]	80.11	155	182.6		142.2		139.1	166	70.5	145	20.2	130
7[b]	79.95	163	186.6		125.4	171	153.1	163	68.9	148	18.2	130
8[b]	80.25	162	180.8		118.3		153.0	164	70.14	153	18.1	130
10[c]	78.8	164	130.7	170	145.3		185.5		78.5	146	61.9	150, 139
11[b]	80.83	141	134.4	162	145.6		187.0		78.8	145	61.2	150, 140
12[c]	79.0	163	134.1	161	145.6		188.3		76.9	143	15.2	130
13[b]	79.26	167	143.8	168	130	170	194.0		79.2	145	15.2	130

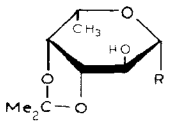
[a]δ in p.p.m., J in Hz. [b]Solution in $CDCl_3$. [c]Solution in C_6D_6.

TABLE II

N.M.R. DATA[a] FOR UNSATURATED KETONUCLEOSIDES

	^{1}H-N.m.r. data											
	H-1'	$J_{1',2'}$	*H-2'*	$J_{2',3'}$	H-3'	$J_{3',4'}$	H-4'	$J_{4',5'}$	H-5'	$J_{5',6'a}$	$J_{5',6'b}$	*H-6'*
1[b]	5.87	7.3	4.17	6.0	4.30	6.0	3.99	6.0	3.56	6.0		1.40
3[b]	6.69				4.77	5.4	4.55	0	4.49	6.6		1.47
2[b]	5.60	8.4	4.69	5.8	4.33	5.9	4.12	6.6	3.83	7.3		1.38
4[b]	6.21				4.69	5.5	4.49	0	4.44	6.5		1.45
9[b]	4.98	11.0	4.67	11.9	4.39				4.27	8.5	5.2	3.31–3.58
	^{13}C-N.m.r. data											
	C-1'	$J_{C-1',H-1'}$	*C-2'*	$J_{C-2',H-2'}$	*C-3'*	$J_{C-3',H-3'}$	*C-4'*	$J_{C-4',H-4'}$	*C-5'*	$J_{C-5',H-5'}$	*C-6'*	$J_{C-6',H-6'}$
1[b]	85.2	158	78.6	161	75.6	155	72.6	148	71.9	126	16.3	129
3[c]	80.6	169	197.2		82.9	163	77.6	150	71.8	139	16.0	128
2[b]	85.2	158	78.9	150	76.1	148	71.7	142	71.4	145	16.4	126
4[b]	82.0	149	198.8		80.4	155	79.8	151	72.1	140	16.5	130
9[b]	83.7	141	79.4	140	139.3	180	199.6		84.2	161	61.7	150, 140

[a]δ in p.p.m., J in Hz. [b]Solution in $CDCl_3$. [c]Solution in C_6D_6.



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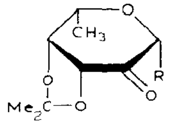
2 R = Thy



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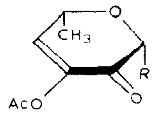

5 R = Th
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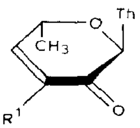
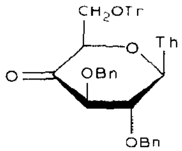


7 R^1 = H
8 R^1 = Br



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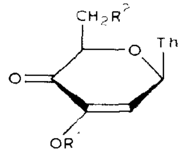
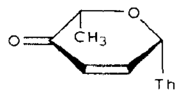


10 R^1 = OAc, R^2 = OAc
11 R^1 = OBz, R^2 = OH
12 R^1 = OBz, R^2 = H



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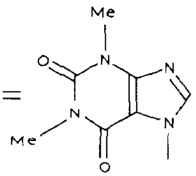
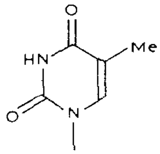
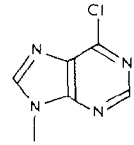
Th = 

Thy = 

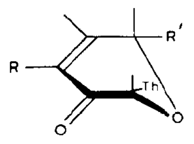
6ClP = 

deshielded, C-1′ is not affected. In 7-(2,3-di-*O*-benzyl-6-*O*-trityl-β-D-*xylo*-hexopyranosyl-4-ulose)theophylline[12] (**9**), where the carbonyl group is at position 4′, C-3′ and C-5′ are markly deshielded and there is an increase in the $^2J_{C,H}$ values. Therefore, the presence of a heterocyclic base α to a keto group blocks the influence of the carbonyl group on the anomeric carbon.

Unsaturated ketonucleosides have half-chair conformations[13] and each of the compounds studied had the bulky theophylline group equatorial[14]. In 7-(3-*O*-acetyl-4,6-dideoxy-β-L-*glycero*-hex-3-enopyranosyl-2-ulose)theophylline[15] (**5**) and 9-(3-*O*-acetyl-4,6-dideoxy-β-L-*glycero*-hex-3-enopyranosyl-2-ulose)-6-chloropurine[16] (**6**), which are both β-L-2′-keto compounds, the purine base and the 5′-substituent are equatorial and conformation **14** is adopted. Long-range coupling ($J_{1',5'}$ 1.5 Hz) was observed for **5** but not for **6**. In addition, C-1′ is more deshielded and $J_{C\text{-}1',H\text{-}1'}$ is smaller in **6** than in **5**, probably because of the higher acidity of the 6-chloropurine moiety.

Conformation **15**, where the 5′-substituent is axial, can be assigned to 7-(3,4,6-trideoxy-α-L-*glycero*-hex-3-enopyranosyl-2-ulose)theophylline[17] (**7**) and 7-(3-bromo-3,4,6-trideoxy-α-L-*glycero*-hex-3-enopyranosyl-2-ulose)theophylline[17] (**8**), which are both α-L compounds. No long-range coupling ($J_{1',5'}$) was observed for these compounds or any allylic coupling for **7**.

7-(3,6-Di-*O*-acetyl-2-deoxy-β-D-*glycero*-hex-2-enopyranosyl-4-ulose)theophylline[18] (**10**), 7-(3-*O*-benzoyl-2-deoxy-β-D-*glycero*-hex-2-enopyranosyl-4-ulose)theophylline[2] (**11**), and 7-(3-*O*-benzoyl-2,6-dideoxy-β-D-*glycero*-hex-2-enopyranosyl-4-ulose)theophylline[2] (**12**) are 4′-keto compounds derived from β-D-glucopyranosyltheophylline. They adopt conformation **16**. This conformation is also adopted by 7-(2,3,6-trideoxy-α-L-*glycero*-hex-2-enopyranosyl-4-ulose)theophylline[19] (**13**). The following allylic coupling constants ($J_{2',5'}$) were determined: **10** 1.7, **11** 1.8, **12** 1.5, and **13** 1.7 Hz. A $J_{1',3'}$ value of 2.1 Hz was also observed for **13**.



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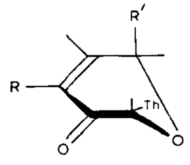

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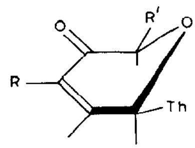

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EXPERIMENTAL

^{1}H-N.m.r. (300 MHz) and ^{13}C-n.m.r. (75 MHz) spectra (internal Me_4Si) were recorded at room temperature with a Bruker 300 MSL spectrometer. For ^{1}H-n.m.r. spectra, the acquisition time was 2 s and the pulse width was 40°. For ^{1}H-decoupled ^{13}C-n.m.r. spectra, the acquisition time was 1 s and the pulse width was 20°. The gated-decoupling technique was used for the measurement of ^{13}C–^{1}H couplings. When necessary, assignments of signals were confirmed using heteronuclear-correlated 2D spectrometry (XHCORD pulse sequence). The precisions estimated for δ and J values were ^{1}H, 0.02 p.p.m. and 0.2 Hz; ^{13}C, 0.2 p.p.m. and 1 Hz.

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REFERENCES

1 K. Antonakis and I. Chouroulinkov, *Biochem. Pharmacol.*, 23 (1974) 2095–2100.
2 K. Antonakis, T. Halmos, J. Bach, and I. Chouroulinkov, *Eur. J. Med. Chem. Chim. Therapeut.*, 15 (1980) 237–240.
3 M. A. Alaoui-Jamali, M. J. Arvor-Egron, M. Bessodes, K. Antonakis, and I. Chouroulinkov, *Eur. J. Med. Chem.*, 22 (1987) 305–310.
4 M. A. Alaoui-Jamali, C. Lasne, K. Antonakis, and I. Chouroulinkov, *Mutagenesis*, 6 (1986) 411–417.
5 C. Aujard, Y. Moule, E. Chany-Morel, and K. Antonakis, *Biochem. Pharmacol.*, 27 (1978) 1037–1042.
6 T. Halmos, A. Cardon, and K. Antonakis, *Chem.-Biol. Interactions*, 46 (1983) 11–29.
7 K. Antonakis, *Carbohydr. Res.*, 24 (1972) 229–234.
8 J. Herscovici, M. J. Egron, and K. Antonakis, *J. Chem. Soc., Perkin Trans 1*, (1982) 1967–1973.
9 B. Coxon, *Methods Carbohydr. Chem.*, 6 (1972) 513–539.
10 B. Coxon, *Carbohydr. Res.*, 13 (1970) 321–330.
11 J. Tronchet, F. Barbalat-Rey, and J. Chalet, *Carbohydr. Res.*, 30 (1973) 229–238.
12 T. Halmos and K. Antonakis, unpublished results.
13 E. F. L. J. Anet, *Carbohydr. Res.*, 1 (1966) 348–356.
14 K. Antonakis, *Adv. Carbohydr. Chem. Biochem.*, 42 (1984) 227–264.

15 K. ANTONAKIS AND M. J. ARVOR-EGRON, *Carbohydr. Res.*, 27 (1973) 468–470.
16 K. ANTONAKIS AND M. BESSODES, *Carbohydr. Res.*, 30 (1973) 192–195.
17 J. HERSCOVICI AND K. ANTONAKIS, *J. Chem. Soc., Perkin Trans 1,* (1979) 2682–2686.
18 T. HALMOS AND K. ANTONAKIS, *Carbohydr. Res.*, 68 (1979) 61–69.
19 J. HERSCOVICI, J. M. ARGOULLON, M. J. EGRON, AND K. ANTONAKIS, *Carbohydr. Res.*, 112 (1983) 301–306.