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THERMAL AND SPECTRAL STUDY OF 5-CHLORO-4-β-D-(*o*-ACETYL)-GLYCOPYRANOSYLAMINOPYRMIDINE DERIVATIVES

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ABSTRACT

Seven 5-chloro-4-β-D-glycopyranosylaminopyrimidine derivatives have been characterized by elemental analysis, IR and ^{1}H-NMR spectroscopies. Four types of process were characterized from the thermal study of the compounds: desolvations; solid–solid transitions; melting; and the onset of pyrolitic decomposition, which consists of deacetylation. In some of the compounds, deacetylation occurs together with the loss of $-OCH_3$ substituents on the C–2.

INTRODUCTION

Many pyrimidine derivatives and some of their nucleosides show biological activity [1,2]; in particular, several 5-halogenopyrimidine derivatives and some of their nucleosides are active in important biological processes [1,13] besides being important intermediates in 5-substituted pyrimidine-derivative syntheses [4].

On the other hand, the synthesis of metal complexes with nucleoside analogues as ligands is of great importance for two reasons. Firstly, the structural study of these complexes provides valuable stereochemical data on the metal ions (many of which exhibit biological activity) [5]; and secondly, the possible anti-tumour activity of the complex is often enhanced in relation to that of the free ligand [6–9].

The data presented in this paper are concerned with the group of nucleoside analogues shown below and should be useful in the subsequent testing of such compounds as possible ligands against transition metal ions.

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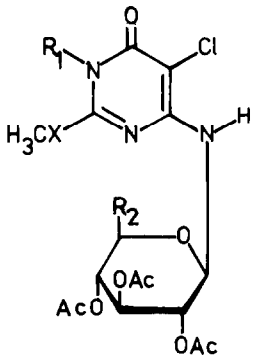

COMPOUND	X	R_1	R_2
A	O	H	CH_2OAc
B	O	CH_3	H
C	O	CH_3	CH_2OAc
D	S	H	H
E	S	H	CH_2OAc
F	S	CH_3	H
G	S	CH_3	CH_2OAc

Formula 1.

EXPERIMENTAL

The seven compounds were synthesized by a previously reported method and recrystallized from methanol. Their in vivo anti-cancer activities, as L1210 inhibitors, have been measured in the National Cancer Institute of Bethesda (MD, U.S.A.) [10].

The compounds were analyzed in the Instituto Nacional de Química Orgánica (CSIC, Madrid) and the data are listed in Table 1.

TABLE 1

Analytic and yield data

Compound	C(%)	H(%)	N(%)	Formula	Yield (%)
A	44.95 (45.11)	4.91 (4.78)	8.41 (8.31)	$C_{19}H_{24}N_3O_{11}Cl$	68
B	45.55 (45.59)	5.02 (4.95)	9.42 (9.38)	$C_{17}H_{22}N_3O_9Cl$	54
C	46.41 (46.21)	4.99 (5.04)	8.07 (8.08)	$C_{20}H_{26}N_3O_{11}Cl$	74
D	42.77 (42.68)	4.63 (4.48)	9.36 (9.34)	$C_{16}H_{20}N_3O_8Cl$	85
E	43.67 (43.72)	4.59 (4.64)	7.84 (8.05)	$C_{19}H_{24}N_3O_{10}SCl$	70
F	44.17 (44.02)	4.87 (4.78)	8.96 (9.06)	$C_{17}H_{22}N_3O_8SCl$	77
G	44.66 (44.82)	4.94 (4.89)	7.80 (7.84)	$C_{20}H_{26}N_3O_{10}SCl$	80

The analytical data in parentheses are theoretical values.

^{1}H-NMR spectra were obtained from a Hitachi Perkin–Elmer R-600 FT spectrometer using DMSO-d_6 as solvent and TMS as internal standard. IR spectra were obtained using samples of the compounds in KBr pellets using a Beckman 4250 spectrophotometer.

DSC plots were obtained with a Mettler DSC-20 differential scanning calorimeter at a heating rate of 5 °C min^{-1}, with samples of 1.02–1.18 mg. TG curves were obtained from a Mettler TG 50 thermobalance, in a static pure air atmosphere, at a heating rate of 10 °C min^{-1}, using samples of 9.74–13.00 mg.

RESULTS AND DISCUSSION

Spectral study

The IR spectra of the compounds under study are fairly similar to those of 5-unchlorinated homologues which were previously reported [10]. The assignments of the most significant bands of these spectra are collected in Table 2.

The band assigned to ν(OH) stretching in compound F is because of 2.5% methanol absorbed into the sample. The wavenumbers of the bands assigned to $\nu(C{=}O)_{acetate}$, $\nu(C{=}O)_{oxo}$, ν(C=N), ν(C=C), ν(C–N) and ν(C–O) are very similar to the corresponding unchlorinated homologues, although the wavenumber of $\nu(C{=}O)_{oxo}$ stretching appears systematically shifted to higher values than in the 5-unchlorinated compounds. This fact could be explained by an increase in the electronic density in the pyrimidine ring induced by the Cl atom on the C–5 position.

On the other hand, the band assigned to $\nu(C{=}O)_{acetate}$ stretching appears as a doublet in several of the compounds, which could be related to the hydrogen bridge interaction between the $C{=}O_{acetate}$ group and the C(4)–NH of the pyrimidine ring.

Another significant fact is the disappearance, in the 5-unchlorinated compounds, of the band centered between 3010 and 3030 cm^{-1} values, which corresponds to ν(C(5)–H) stretching.

The accurate assignment of characteristic bands of the C(5)–Cl bond was prevented because of the high absorption of the compounds in the ranges between 400 and 500 cm^{-1} and 200 and 300 cm^{-1}, in which characteristic C–Cl stretching and bending, respectively, should appear [11–4].

Signal values of ^{1}H-NMR spectra of the compounds have been reported previously [15]. The said spectra are very similar to those of the corresponding 5-unchlorinated homologues except for the absence of the singlet corresponding to the C(5)–H group in the compounds under study. Besides, it is interesting to point out two features about the spectra, namely: (a) the C(4)–NH signal appears as a doublet (δ values between 7.10 and 7.30 ppm)

TABLE 2

IR spectra data (ν, cm^{-1})

Compound	ν(OH)	ν(N–H)	ν(C–H)	ν(C=O)$_{acetate}$	ν(C=O)$_{oxo}$	ν(C=N) + ν(C=C)	ν(C–N) + ν(C–O)
A		3400 w	2950 w	1745 s	1670 s	1620 s	1035 wd, s
			2880 w			1590 s	1210–1260 s,b
B		3360 w	2960 w	1740 s	1685 s	1620 s	1030 m
			2880 w	1750 s		1560 s	1065 s
							1080 m
							1225 wd,s
							1260 s
							1275 m
C		3400 w	2940 w	1750 s	1690 s	1620 s	1035 s
				1730 s		1570 s	1070 m
							1080 m
							1210–1260 s,b
D		3400 w	2940 w	1750 [a]s	1670 s,b	1600 s	1040 s
			2850 w			1550 m	1260 m
							1070 m
							1210–1260 s,b
E		3400 w	2930 w	1745 s	1665 s	1595 s	1035 b,s
						1545 m	1225 b,s
							1250 s
F	3490 w	3410 m	2940 w	1735 [a]s	1675 s	1600 s	1025 s
			2860 w			1525 s	1045 s
							1070 s
							1230 b,s
							1255 s
G		3410 w	2950 w	1755 s	1685 m	1610 s	1040 s
						1535 m	1070 m
							1210–1260 s,b

w, weak; m, medium; s, strong; wd, wide; b, broad.

[a] Doublet band.

due to the coupling with the C(1′)–H of the pyranosic ring ($J_{NH,C(1')-H} = 8.2$ Hz). This doublet disappears when D_2O was added to the DMSO-d_6 solution of the compound studied. The δ values of the C(4)–NH doublet suggest there are no inter- or intramolecular hydrogen bridge interactions in which this group takes part; when such interaction occurs, the δ values are considerably higher, e.g. this signal appears at about 11.00 ppm in the 5-acetyl-4-β-D-glycopyranosylaminopyrimidine derivative homologues [16] and at 12.25–12.70 ppm in the 5-nitroso derivative homologues [17]; in all of them, the C(4)–NH group interacts with the adjacent C(5) substituents (acetyl or NO groups) by hydrogen bridging and (b) the C(1′)–H signal appears as a triplet between 5.50 and 5.90 ppm; this signal becomes a doublet when D_2O is added, which is in accordance with the above-cited coupling between C(4)–NH and C(1′)–H groups.

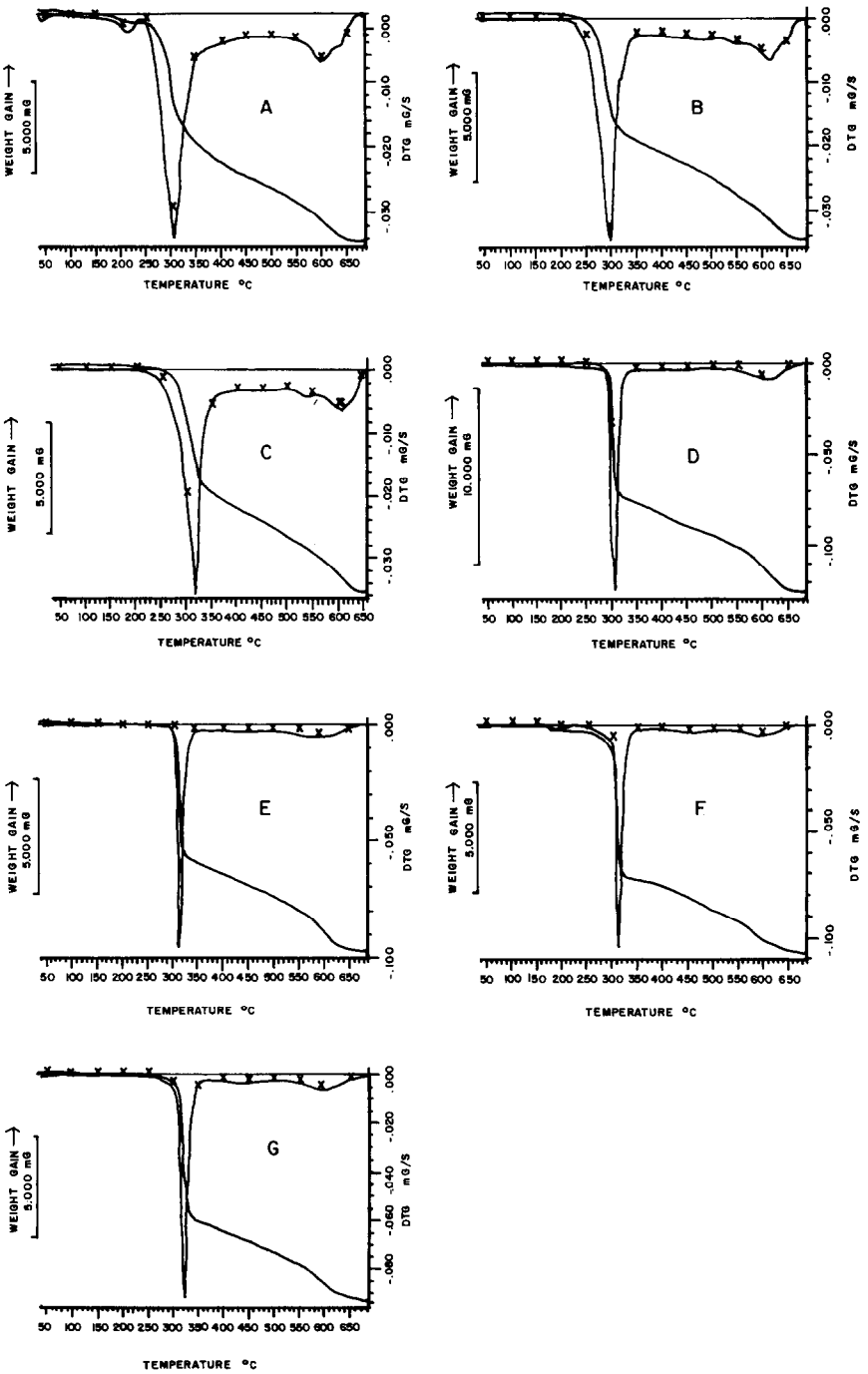

Fig. 1. TG curves.

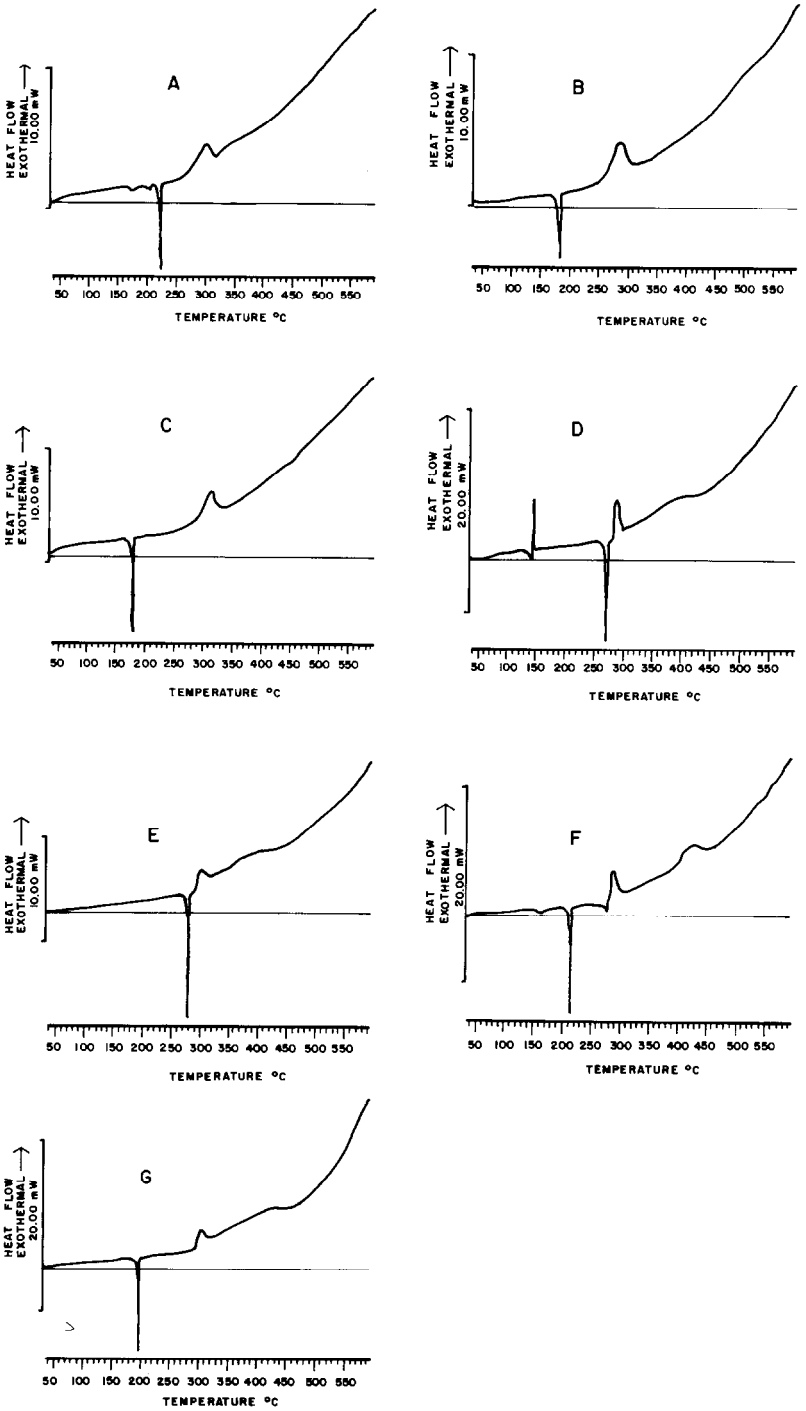

Fig. 2. DSC curves.

TABLE 3

TG and DSC data

Compound	Desolvation			Solid–solid transition		Melting [a]		Start of pyrolisis	Deacetylation	
	T (°C)	Wt. loss (%)	ΔH (kJ mol^{-1})	T (°C)	ΔH (kJ mol^{-1})	T (°C)	ΔH (kJ mol^{-1})	T (°C)	T (°C)	ΔH (kJ mol^{-1})
A				174, endo	−3.2	223.5	32.46 [b]	190	199, exo	−62.8
B						183.7	24.55	210	284, exo	−85.3
C						180.4	36.86	205	314, exo	−87.8
D	142	1.5	8.6	146, exo	−14.9	273.1	46.05 [b]	270	289, exo	−29.9
E						280.1	55.92	285	298, exo	−48.8
F	162	2.5	7.2			215.2	40.27	240	290, exo	−27.7
G						199.0	42.56	240	305, exo	−45.9

[a] Temperatures correspond to the peak of the endothermic.

[b] The endothermic overlaps with the start of the pyrolisis.

Thermal study

The TG and DSC curves of the seven compounds are very similar (Figs. 1 and 2, respectively); the thermal data obtained from them are listed in Table 3.

The DSC curves of compounds D and F show a first endothermic effect (at temperature values of 146 and 162° C, respectively) accompanied by a slight weight loss which is due to desolvation of the samples. Compounds A and D show endothermic effects at temperatures of 174 and 146° C, respectively, at these temperatures no weight loss occurs. Samples of A and D were heated up to the end temperatures of the said effects and their DSC plots were obtained again after several hours, but the above-cited effects were not observed; therefore, they can be assigned to probable solid–solid transitions. Nevertheless, IR spectra of the heated samples were identical to those of the unheated.

Melting

All the compounds show melting processes before the pyrolitic decomposition whose corresponding endothermic effects (energies and temperatures) are summarized in Table 3. The melting temperatures are slightly higher than those of the corresponding homologue with $-COCH_3$ substituted on the C(5) of the pyrimidine ring [16] and much higher than those with no substituents on the C(5) [10]; this would mean that chlorine atoms on the C(5) play an important role in intermolecular hydrogen bridging interactions.

On the other hand, in the series of compounds under study with the same substituent on the C(2) of the pyrimidine ring (OCH_3 or SCH_3), the highest melting point corresponds to the compounds having no substituent on N(1) of the pyrimidine ring; this suggests the probable role of this atom in intramolecular hydrogen bridges.

ΔH_{fusion} values are in the same range as those found for other analogous compounds [10,16]. Nevertheless, in the case of compound A the melting process coincides with the onset of its pyrolitic decomposition, as can be seen in the corresponding TG curve; thus, in this case, the endothermic effect corresponding to the fusion probably hides some other thermal effect whose energy could be partially included in the corresponding value given in Table 3.

Pyrolitic decompositions

TG and DSC curves of the compounds under study are very similar to those of their homologues which have no substituent on (C(5), suggesting that the pyrolitic decompositions start with loss of the acetyl groups [10].

TABLE 4

Weight loss of the deacetylation processes (%)

Compound	Found	Calculated
A	52.90 (52.81)	46.69
B	46.21 (45.90)	39.55
C	52.12 (51.39)	45.42
D	38.15	39.37
E	47.58	45.25
F	36.80	38.18
G	45.46	44.07

Values in parentheses are those calculated including OCH_3 groups.

The onset of pyrolitic decomposition is characterized, in all cases, by an abrupt weight loss in the TG plots, accompanied by a well-defined exothermic effect in the corresponding DSC diagram. IR spectra from samples obtained by heating up to the final temperature of the said effect clearly show (in spite of the low resolution due to the partial carbonization of the samples) the loss of the band assigned to $\nu(C{=}O)_{acetate}$ corresponding to the acetyl groups; the weight loss values found from the TG curves (%) at the said temperatures are in good agreement with the calculated ones (Table 4) for acetyl groups in the case of compounds having SCH_3 substituents on the C(2) (compounds D, E, F and G), but are slightly higher than those corresponding to compounds with OCH_3 substituents on the C(2); thus, in the latter cases, it may be that some other group is also being lost together with the acetyl groups; however, no such evidence could be obtained from the IR spectra. Water solutions of previously deacetylated mineralized samples (with solid Na) of compounds A, B and C, precipitate AgCl which suggests that Cl groups probably remain unaffected. So, the group lost together with the acetyl could be OCH_3 (see Table 4); this is in accordance with the previously observed lability of the C(s)–OCH_3 bond in some analogous pyrimidine derivatives [18]. Moreover, this could explain the lower temperature values for the onset of the pyrolitic decomposition of compounds A, B and C (see Table 3) than for the remaining ones.

The ΔH values for deacetylation processes (see Table 3) are in a clearly higher range for compounds A, B and C, than for D, E, F and G; this fact also supports the above hypothesis that the deacetylation process coincides with the loss of the OCH_3 groups in the former compounds.

After deacetylation, the thermal decomposition of the compounds goes on uninterrupted until the total combustion of the samples, which occurs at about 650 °C.

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