Infrared Absorption Spectra of a Series of 2, 6-diamino and 2-amino-6-hydroxy-8-choroalkyl Purines

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INTRODUCTION

Purines 1 and derivatives 2, 3, and 4 are in use in medicine as drugs (Daly 1985). Adenosine 2 (a purine nucleoside) is known to demonstrate cardiovascular, nervous and endocrine activities. 8-benzyl theoplyluine 3 has vassopresor activity (Chemical and Eng. News 1986); Brigden et al. (1981), Maylor et al. (1961). Acycloguanosine, 4 (a purine nucleoside (Martins et al. 1985). 2, 6-diamino-8-chloroalkyl purines, 5 and 2-amino-6-hydroxy-8-chloroalkyl purines, 6 are a new series of purines related to the adenosines 2 and unlike adenosines have received limited investigations as therapeutic agents (Ejimadu 1988). It is expected that these new purines will physiologically mimic adenosines or analogs on account of their structural (or 2-amino -6-hydroxy) groups of drugs. C₈ - haloalkyl substituted 2, 6 -diamino (or 2-amino - 6 hydroxy) purines are good alkylating agents for N-nucleophiles (functional group modifying agents, (Ejimadu 1992) and may become good antineoplastiv agents, just like many anticancer alkylators e.g. mitomycins. Their N₉ - if
glycosylated with N₉ sugar analogs 4 may confer anti viral activity on these new purines (Martins 1985; Watt 1990; Schaeffer et al. 1978).

It is therefore significant to present the Infrared spectra of these new purines 5, and 6 which are lacking in the literature.

**MATERIALS AND METHODS**

The melting points were taken on a melting point apparatus and were uncorrected. The ultra violet Imax values were obtained on Beckman DB-9 and infrared (IR) analyses of products were taken on a Nicolet model 700 FTIR interferometer and absorption frequencies reported in cm⁻¹. Elemental analysis (C, H, N) was done by Atlantic Micro Laboratories Inc. Atlanta Georgia, USA.

The following reagents used for reactions were purchased from Aldrich Chemical Company.

a) 2, 6-triamino-4-hydroxy pyrimidine sulphate salt.
b) 2, 4, 5, 6-tetraamino pyrimidine sulphate salt.
c) 4-chlorobutryl chloride
d) 3-chloropropionyl chloride

2, 6-diamino-8-chloromethyl purine 5, \(a=1\)

2, 4, 5, 6-tetra-amino pyrimidine sulphate salt (92.1 g; 0.01 mole) solid was thoroughly mixed in a mortar with chloroacetic acid (4.7 g; 0.05 mole). The mix was taken in a 250 mL round bottom flask. A water aspirator was then attached to this flask (an arrangement to evacuate water produced by the reaction), so as to subject the reaction to some vacuum. The flask with its contents was heated for 2 hrs and allowed to cool. The reaction mixture was washed with diethyl ether (930 mL) for three consecutive times to remove excess (unreacted) chloroacetic acid. The residue was taken in 50 mL of water and filtered (while hot). Fine crystals were obtained on cooling the filtrate. The crystals weighed 0.72 g (32.2% yield).

UV Imax 290 nm at \(pH 11\).

IR (Kbr) \(cm⁻¹\) 3415, 3269, 3154, (-NH₂, -NH)

3020, 2971, 2809 (-CH₂-C₁)

Elemental analysis

Calculated C, 30.71 H, 4.72 N, 35.81 Cl, 15.11

Found C, 30.99 H, 4.92 N, 36.68 Cl, 15.42

Molecular formula: C₁₆H₁₇N₆Cl₂H₂O

2, 6-dimino-8-chloroethyl purines 5, \(n=2\)

2, 4, 5, 6-tetraamino Pyrimidine sulphate- (7 g; 0.08 mole) was dissolved in 2 M NaOH (100 mL) in a 250 mL round bottom flask and an undertermined quantity of ice chips added to the solution. The outside of the reaction flask was also surrounded with ice blocks.

3-chloropropionyl chloride (7 mL; 0.08 mole; 2-equivalents) was added to the flask through an injection needle in two disproportionate batches (4 mL followed by 3 mL later) and vigorously stirred (magnetic stirrer). The flask was stoppered and stirring continued until it became difficult to continue the stirring (because the reaction mixture was very syrupy). The reaction lasted for 20 min and was worked up by filtering with abuchner funnel attached to a powerful water aspirator (to provide sufficient suction pressure). The residue was dissolved in ammonium hydroxide and filtered (hot). A dry weight of crystal of 2.06 g, 20.0% yield. (oven dried at 100°C) was obtained. UV Imax 300nm at \(pH 11\).
INFRARED ABSORPTION SPECTRA OF A SERIES OF PURINES

IR KBr cm⁻¹ 3400, 3344, 3203, 3014 (⁻NH₂⁻ NH) 2956, 2886, 2745 (⁻CH₂⁻Cl)
Elemental analysis:
    Calculated C, 33.81 H, 5.23 N, 33.70 Cl, 14.28
    Found C, 33.59 H, 5.31 N, 33.61 Cl, 14.20
Molecular formula: C₇H₇N₆Cl₂H₂O

2,6-diamino-8-chloropropyl purine, ₂, (n=3)
This compound was made in the same way as for 2,6-diamino-8-chloro ethyl purines ₅, ₉n=2) using 2, 4, 5, 6-tetraamino pyrimidine sulphate salt. 96g; 0.023 mol) and 4-chlorobutryl chloride (0.05 mole; 2 equivalents). A dry weight of 1.66g (31.3% yield) of expected product was obtained after crystallation (hot water).

UV lmax 292nm at pH11.

IR KBr cm⁻¹ 3492, 3386, 3344, 3154 (⁻NH₂⁻NH) 2985, 2942, 2816 (⁻CH₂Cl) Elemental analysis:
    Calculated C, 39.26 H, 5.32 N, 34.35 Cl, 14.15
    Found C, 39.15 H, 5.36 N, 34.98 C1.₁₂91 (b)
\[
\frac{C}{N} \text{ ratio (a)} = 1.14 \\
\frac{C}{N} \text{ ratio (b)} = 1.12
\]
Molecular formula: C₈H₁₀N₅Cl₂

2-amino-6-hydroxyl-8-chloro ethyl purine ₆, (n=2)
2, 5, 6-triamino-4-hydroxy pyrimidine sulphate salt ₁₃ (6g, 0.025 mole) was dissolved in 2M HaOH (50 mL) in 100 mL round bottom flask (with some chips of ice inside and outside the flask as in the case for 2, 6-diamino-8-chloroethyl purine ₅ (n=2)). 2-chloro proponyl chloride ₁₄ (6.24 ml, 0.05 mole, 2-equivalents) was introduced into the flask and stirred. A similar work up procedure was followed as for 5b (n=2). The product obtained weighed 4.07 g (65.02% yield) after hot water recrystallisation ₁₀ UV lmax 292nm at pH11.

IR KBr cm⁻¹ 3400, 3337, (-NH₂;NH) 2858, 2745 (-CH₂-) 744 (-CH₂-C1) Elemental analysis:
    Calculated C, 33.67 H, 4.84 N, 28.05 C1, 14.23
    Found C, 33.34 H, 4.79 N, 27.66 C1, 13.66 (b)
\[
\frac{C}{N} \text{ ratio (a)} = 1.20
\]
Molecular formula: C₈H₁₀ON₅Cl₂ 1/2 H₂O

RESULTS AND DISCUSSION
The infrared absorption spectra of these new agents (Figs. 2, 3, 5 and 6) present definite regional difference with those of related benzimidazoles ⁹ but maintain some semblance with pteridine derivatives (Mowat et al. 1947; Waller 1948; Taylor and Dumas 1982) e.g. 2 – amino – 4 – hydroxy – 6 – methyl pteridines, ⁷, and folic acid, ⁸ (Figs. 7 and 4). Hitchings et al. (1949).

Hydrogen bonding between N₇ and N₉ positions of neighbouring purines has been put forward to rationalize the high melting point of purines (213°C) lin, T et al. (1984). The purines were therefore thought to exist as chains of molecules (in the solid phase) because of the extensive hydrogen bonding. Hydrogen bonding of the kind N-H ...N has been used to explain the absence of absorption in the normal stretching region (i.e. 3400 cm⁻¹) in benzimidazoles, ⁹ (close relatives of the purines) in solid specimens (Morgan 1961) (Fig. 8). Hydrogen bonding apparently is not operative for these purines in KBr (Potassium bromide).

DISCUSSION
The infrared spectra and bands of these novel compounds (Tables 1, 2, 3 and Figs. 1, 2, 3, 5 and 6) present clear pictures of the N-H stretching region and other regions of the
Fig. 1: IR-absorption spectra of 2,6-diamino-8-chloromethyl purine

Fig. 2: IR-absorption spectra of 2,6-diamino-8-chloroethyl purine

Fig. 3: IR-absorption spectra of 2,6-diamino-8-chloropropyl purine
Fig. 4: Infrared absorption Spectra A. Natural Liver L. Casei factor B. Synthetic Liver L. Casei factor or (pteroyglutamic acid) C. Synthetic racemic Liver L. Casei factor (racemic pteroylglutamic acid); D. Natural racemic Liver L. Casei factor E. Pteroic acid. (II)

Fig. 5: IR-absorption spectra of 2-amino-6-hydroxy-8-chloroethyl purine (Guanine)

Fig. 6: IR-absorption spectra of 2-amino-6-hydroxy-8-chloroprophyl purine (Guanine)
TABLE 1
IR absorption bands and melting point of 2, 6-diamino-8-chloroalkyl purines (3000-4000 cm⁻¹)

<table>
<thead>
<tr>
<th>n</th>
<th>IR cm⁻¹ (KBr)</th>
<th>m.p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3415, 3337, 3269, 3154, 3020 - NH₂, -NH</td>
<td>300°C</td>
</tr>
<tr>
<td>2</td>
<td>3400, 3344, 3202, 3147 - NH₂, -NH</td>
<td>300°C</td>
</tr>
</tbody>
</table>

TABLE 2
IR absorption bands and melting point of 2-amino-6-hydroxy-8-chloroalkys purines (3000-4000 cm⁻¹)

<table>
<thead>
<tr>
<th>n</th>
<th>IR cm⁻¹ (KBr)</th>
<th>m.p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2971, 2809, 1647, 1618, 1590, 1569, 1520, 1492, 1449, 1435, 1400, 1315, 1259, 1238, 1202, 1100, 1020, 981, 963, 780, 710, 639</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2956, 2886, 2745, 2661, 1660, 1618, 1561, 1498, 1449, 1399, 1378, 1308, 1272, 1202, 1160, 1019, 984, 934, 892, 786, 709, 666</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2985, 2942, 2921, 2816, 1646, 1611, 1561, 1498, 1449, 1371, 1285, 1299, 1174, 1146, 1089, 1005, 984, 927, 899, 843, 786, 666</td>
<td></td>
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</tbody>
</table>

TABLE 3
Other bands (3000 – 600 cm⁻¹) diagram
INFRARED ABSORPTION SPECTRA OF A SERIES OF PURINES

The normal N-H bands at 3400 cm\(^{-1}\) are unaffected by the medium in which these purines were dispersed for their infrared spectral determinations (i.e. K\(_\text{Br}\)). This band (3400 cm\(^{-1}\)) is seen only in solutions of benzimidazole spectra. The spectra of benzimidazoles is known to cause no significant change in benzimidazole spectra. The spectra of these purines 5-9a, b, c) are being reported for the first time. It is interesting to note that the region of the spectra 3000-4000 cm\(^{-1}\) are similar in both the purines (e.g. 2-amino-6-hydroxy derivatives, Figs. 5, 6) and in the pteridine series 9pteroyl glutamic acid – Fig. 4, and 2-amino – 4-hydroxy-6-methyl pteridine- Fig. 7; Waller et al. (1948); Wein Stock et al. (1970).

The replacement of 6-OH group (in the pteridines) with –NH\(_2\) group does not create a marked difference in the shape of the spectra (even though –OH and –NH\(_2\) groups absorb at different frequencies).

The contrast in the shape of the spectra in this region (3200 to 4000 cm\(^{-1}\)) for the diamino or amino – hydroxy purines and the benzimidazole is a consequence of replacement of pyrimidine component (fused to imidazole in benzimidazole – Figs. 1, 2, 3, 5, 6 compared with Fig. 8).

The melting point for purines 5 and 6 are high and range from 259-300°C. The purines melt lower (140°C).

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REFERENCES


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