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

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**ABSTRACT**

8-haloalkyl disintesikan dan diuji dengan menggunakan analisis inframerah (IR). Sintesis dan analisis inframerah tersebut dicatatkan. Kajian ke atas purina tersebut merangkumi (i) 2,6-diamino-8-purinaklorometil, (ii) 2,6-diamino-8-purinalekotil, (iii) 2,6-diamino-8-purina kloroprofil, (iv) 2-amino-6-hidroksil-8-purina korotil, (v) purina 2-amino-6-hidroksil 8 purina (3-kloroprofil). Penyeraapan lmax ultra ungu terhadap purina tersebut dibintangkan pada dan keputusanannya dibentangkan. Tahap kecairan dan elemen analisisnya turut dibentangkan. Spektra inframerah (inframerah dalam KBr) C-8 diganti 2, 6-diamino; 5 atau 2-amoni 6-purina hidrosil, 6 dibandingkan dengan 7 inframerah pteridin; 8; benzimidazola, 9; pirrols, 10; indole, 11 (jadual I, II, III dan rajah 1, 2, 3, 4, 5 dan 6). Rajah 4 dibentangkan untuk dikaitkan purina baru tersebut dengan (i) hati semula jadi L. faktor casei, (A) (ii) hati sintetik L. faktor casei (asid Rasemik pteroylgutamik (C) (v) hati sintetik rasemik L. faktor casei, asid petrylgutamik rasemik (D) (iv) Hati rasemik semula jadi L. casei faktor asid pteroik (E).

**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 theopylluine 3 has vassopresor actvity (Chemical and Eng. News 1986); Brigden et al. (1981), Maylor et al. (1961). Acycloguanosine, 4 (a purine nucleocide (Martins et al. 1985). 2, 6-diamino-8-chloraalkyl purines, 5 and 2-amino-6-hydroxy-8-chloraalkyl 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 – haloakyl substituted 2, 6 –diamino (or 2-amino – 6 hydroxy) purines are good alkylating agents for N-nucophiles (functional group modifying agents, (Ejimadu 1992) and may become good antineoplastiv agents, just like many anticancer alkylators e.g. mitomycins. Their N₉ – if
2, 6-diamino-8-chloromethyl purine 5, (a=1)
2, 4, 5, 6-tetra-amino pyrimidine sulphate salt (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 $\lambda_{max}$ 300 nm at pH 11.

IR (Kbr) cm$^{-1}$ 3415, 3269, 3154, (-NH$_2$, -NH) 3020, 2971, 2809 (-CH$_2$-Cl)

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: C$_{6}$H$_{7}$N$_{6}$Cl$_{2}$H$_{2}$O

2, 6-dimino-8-chloroethyl purines 6, (n=2)
2, 4, 5, 6-tetra-amino 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 $\lambda_{max}$ 300nm at pH 11.
INFRARED ABSORPTION SPECTRA OF A SERIES OF PURINES

\[ \text{IR KBr cm}^{-1} 3400, 3344, 3203, 3014 (-NH_2; -NH) 2956, 2886, 2745 (-CH}_2 C1) \]

Elemental analysis:
- Calculated: C, 33.81 H, 5.23 N, 33.70 C1, 14.28
- Found: C, 33.59 H, 5.31 N, 33.61 C1, 14.20
- Molecular formula: C_{n+2}H_{2n}N_{n}Cl_{1.2}H_2O

2,6-diamino-8-chloroethyl purine, \( \_5 \) (n=3)
This compound was made in the same way as for 2,6-diamino-8-chloroethyl purines 5, 9n=2) using 2, 4, 5, 6-tetraamino pyrimidine sulphate salt (9g; 0.025 mole) and 4-chlorobutyl chloride (0.05 mole; 2 equivalents). A dry weight of 1.66g (31.3% yield) of expected product was obtained after crystallization (hot water).

UV \( \lambda_{max} \) 292nm at pH11.

IR KBr cm-1 3492, 3386, 3 344, 3154 (-NH2; -NH) 2985, 2942, 2816 (-CH2C1), Elemental analysis:
- Calculated: C, 39.26 H, 5.32 N, 34.35 C1, 14.15 (a)
- Found: C, 39.15 H, 5.36 n, 34.98 C1,, 1291 (b)

\( \frac{C}{N} \) ratio(a) = 1.14

\( \frac{C}{N} \) ratio(b) = 1.12

Molecular formula: C_{n+1}H_{2n}N_{n}Cl_{1.2}H_2O

2-amino-6-hydroxy-8-chloroethyl 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

UVmax 292nm at pH11.

IR KBr cm-1 3400, 3337, (NH2;NH) 2858, 2745 (-CH2) 744 (-CH3C1) 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)

\( \frac{C}{N} \) ratio(a) = 1.20

\( \frac{C}{N} \) ratio(b) = 1.20

Molecular formula: C_{n+1}H_{2n}N_{n}Cl_{1.2}H_2O

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, folic acid, (Figs. 7 and 4). Hitchings et al. (1949).

Hydrogen bonding between N, and N, 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
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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-chlorophenyl 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>
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<tbody>
<tr>
<td>1</td>
<td>3415, 3337, 3269, 3154, 3020</td>
<td>- NH₂-NH</td>
</tr>
<tr>
<td>2</td>
<td>3400, 3344, 3202, 3147</td>
<td>NH₂-NH</td>
</tr>
</tbody>
</table>

TABLE 2
IR absorption bands and melting point of 2-amino-6-hydroxy-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>- - -</td>
<td>- - -</td>
</tr>
<tr>
<td>2</td>
<td>3464, 3450, 3339, 3281, 3125</td>
<td>- OH, -NH₂, 300 C</td>
</tr>
<tr>
<td>3</td>
<td>3450, 3393, 3380, 3374, 3168, 3006</td>
<td>-OH, 300 C</td>
</tr>
</tbody>
</table>

TABLE 3
Other bands (3000 - 600 cm⁻¹) diagram

A

B

cont. TABLE 3

<table>
<thead>
<tr>
<th>n</th>
<th>IR cm⁻¹ KBr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2971, 2928, (-CH₃), 1681, 1632, 1575, 1484, 1449, 1406, 1315, 1237, 1216, 1153, 1012, 927, 892, 772, 702, (-CH₃Cl), 652</td>
</tr>
<tr>
<td>2</td>
<td>2971, 2935, (CH₂), 1681, 1632, 1575, 1484, 1449, 1408, 1348, 1300, 1237, 1209, 1106, 1012, 989, 778, 695, (-CH₃Cl), 652</td>
</tr>
</tbody>
</table>
INFRARED ABSORPTION SPECTRA OF A SERIES OF PURINES

different molecules. 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. KBr). This band (3400 cm\(^{-1}\)) is seen only in solutions of benzimidazole spectra. The spectra 9.1 mole/L 9, pyrroles 10 and indoles, 11 as simple in the region 2400-3200 cm\(^{-1}\) for solid specimens (e.g. Fig. 8) (Morgan 1961). The use of KBr (for 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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