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

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Keywords: Infrared analysis, purines, synthesize, melting point, absorption spectra

ABSTRAK

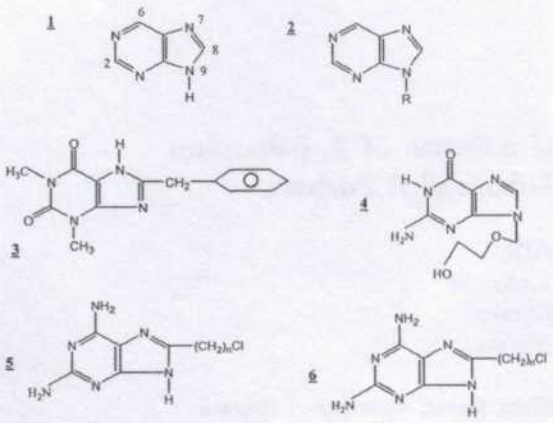
8 purina haloalki disintesiskan dan diuji dengan menggunakan analisis inframerah (IR). Sintesis dan analisis inframerah tersebut dicatatkan. Kajian ke atas purina tersebut merangkumi (i) 2,6-diamino-8-purina-Klorometil, (ii) 2,6-diamino-8-purina kloretil, (iii) 2,6-diamino-8-purina kloroprofil, (iv) 2-amino-6-hidroksil-8-purina korotil, (v) purina 2-amino-6-hidroksil 8 purina (3-kloroprofil). Penyerapan Imax ultra ungu terhadap purina tersebut diambil pada $_{P}^{H11}$ dan keputusannya dibentangkan. Tahap kecairan dan elemen analisisnya turut dibentangkan. Spektra inframerah (inframerah dalam KBr) C-8 diganti 2, 6-diamino; 5 or 2-amoni 6-purina hidroksi, 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).

ABSTRACT

8-haloalky purines were synthesized and infrared analysis (IR) carried out on them. The syntheses as well as the IR analyses are reported. The purines synthesized and studied include (i) 2,6-diamino-8-Chloromethyl purines, (ii) 2,6-diamino-8-chlorethyl purine, (iii) 2,6-diamino-8-chloropropyl purine, (iv) 2-amino-6-hydroxyl-8-chloroethyl purine, (v) 2-amino-6-hydroxyl 8-(3-chloropropyl) purine. The ultra violet UV lmax absorption of these purines were taken at $_{P}^{H11}$ and results are presented. The melting points and their elemental analyses are also presented. The IR (infrared in KBr) spectra of C-8 substituted 2, 6-diamino; 5 or 2-amino –6hydroxy purines, 6 are compared to the IR spectra of pteridines 7; 8; benzimidazole, 9; Pyrroles, 10; indole, 11 (Tables I, II, III and figures 1, 2, 3, 5 *and* 6*). Figure 4 is presented to relate these novel purines to (i) natural liver L. casei factor (A) (ii) synthetic liver L. cacei factor (Racemic pteroylgutamic acid (C) (v) Synthetic racemic liver L. casei factor, racemic pteroylglutamic acid (D) (iv) Natural racemic liver L. casei factor pteroic acid (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-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. C_8 – haloakyl substituted 2, 6 –diamino (or 2-amino – 6 hydroxy) purines are good alkylating agents for N-nuceophiles (functional group modifying agents, (Ejimadu 1992) and may become good antineoplastiv agents, just like many anticancer alkylators e.g. mitomycins. Their N_9 – if



SYNTHESIS

14 n=2

15 n=3

5a: R1 = R2 = NH2 (n=1) **5b:** R1 = R2 = NH2 = (n =2)

5c: R1 = R2 = NH2 (n=3)

6a: R1 = OH; R2 = NH2 (n=2) **6b:** R1 = OH; R2 = NH2 (n=2)

12: R1 = R2 = NH2 **13:** R1 = OH; R2 = NH2

14: n = 2 **15:** n = 3

glycosylated with N_9 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 lmax 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-tretraamino pyrimidine sulphate salt.
c) 4-chlorobutyryl chloride
d) 3-chloropropionyl chloride

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

2, 4, 5, 6-tetra-amino pyrimidine sulphate salt 92. 1g,; 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 λmax 290 nm at P^H11.

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 C1, 15.11

Found C, 30.99 H, 4.92 N, 36.68 C1, 15.42

Molecular formula: $C_6H_7N_6C1.2H_2O$

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 lmax 300nm at P^H.11.

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 formular	$C_7H_9N_6C1.2H_2O$

2,6-diamino-8-chloropropyl purine, 5, (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-chlorobutyryl 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 (-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: $C_8H_{11}N_6C1.H_2O$

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**
UVlmax 292nm at pH11.

IR KBr cm^{-1} 3400, 3337, (-NH_2;-NH) 2858, 2745 (-CH_2-) 744 (-CH_2-C1) Elemental analysis:

Calculated	C, 33.67 H, 4.84 N, 28.05 C1, 14.23 9a0
Found	C, 33.34 H, 4.79 N, 27.66 C1, 13.66 (b)

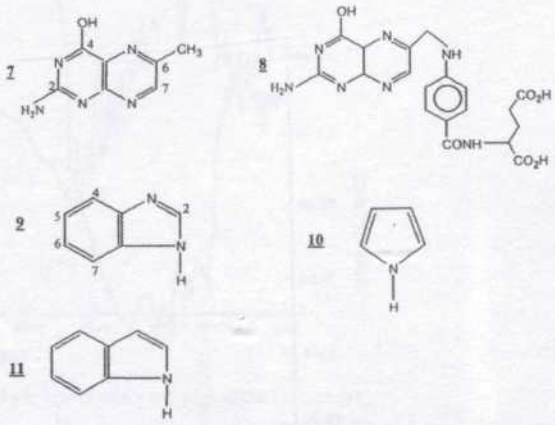
$\frac{C}{N}$ *ratio (a)* = 1.20

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

Molecular formula: $C_8H_{10}ON_5C1.2\ 1/2\ H_2O$

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 benzimdazoles **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 N_7 and N_9 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 benzimdazoles, **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

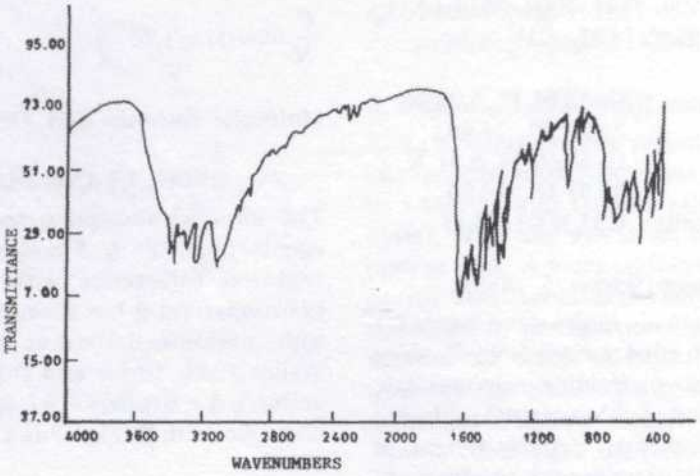


Fig. 1: 1R-absorption spectra of 2,6 – diamino–8–chloromethyl purine

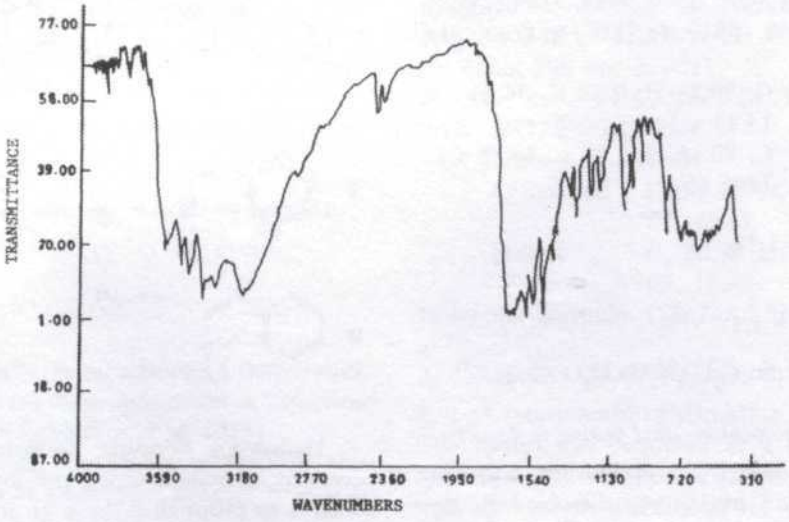


Fig. 2: 1R-absorption spectra of 2,6 – diamino–8–chloroethyl purine

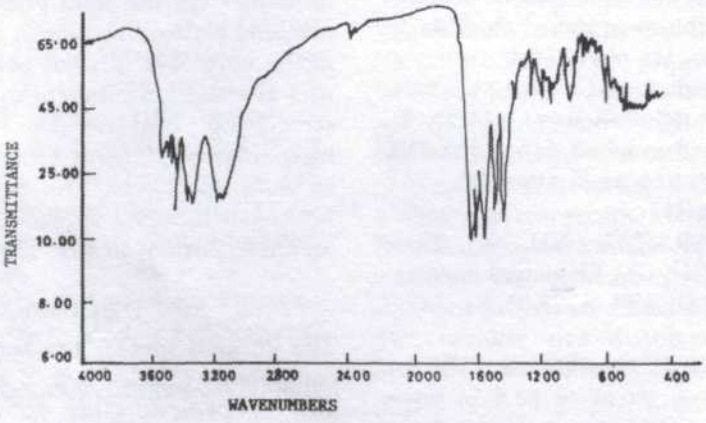


Fig. 3: 1R-absorption spectra of 2,6 – diamino–8–chloropropyl purine

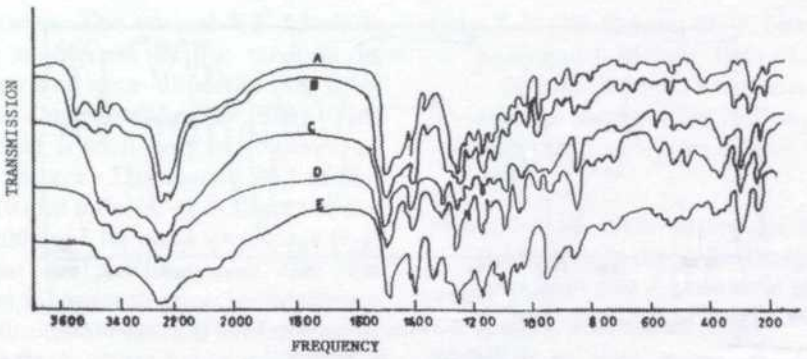


Fig. 4: Infrared absorption Spectra A natural Liver L. Casei factor B. Synthetic Liver L. Casei factor or (pteroyglutamic acid) C. Synthetic racemic Liver L. Casei factor (racemic pteroylglutamic acid); D. natural racemic Liver L. Casei factor E. pteroic acid. (II)

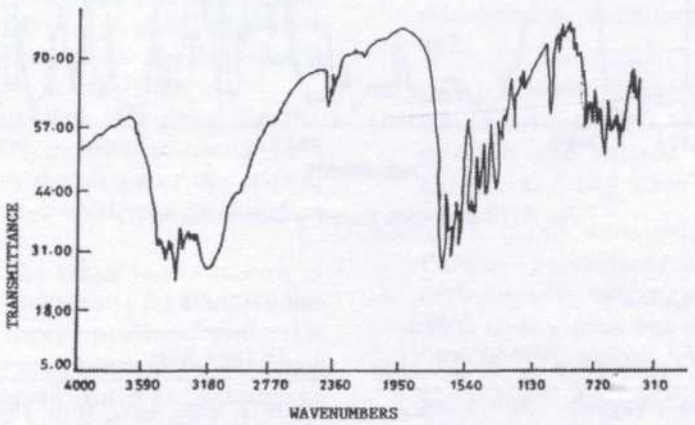


Fig. 5: IR-absorption spectra of 2–amino–6–hydroxy–8–chloroethyl purine (Guanine)

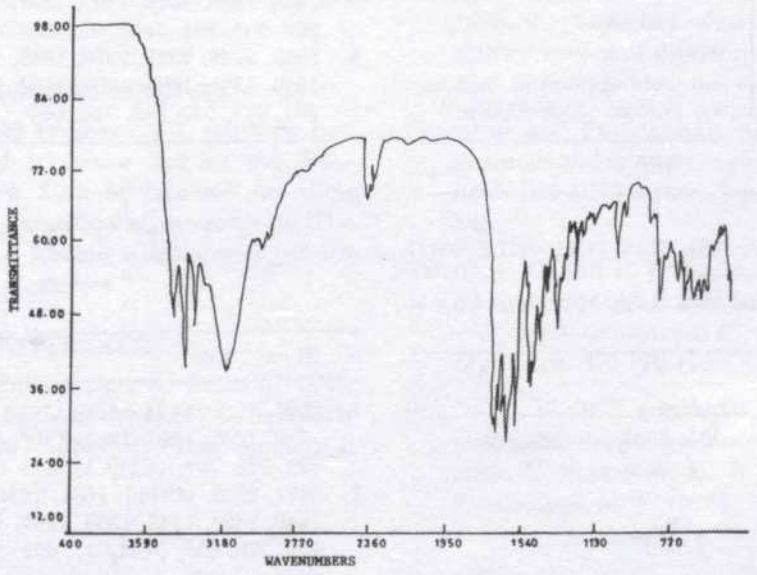


Fig. 6: IR-absorption spectra of 2–amino–6–hydroxy–8–chloroprophyl purine (Guanine)

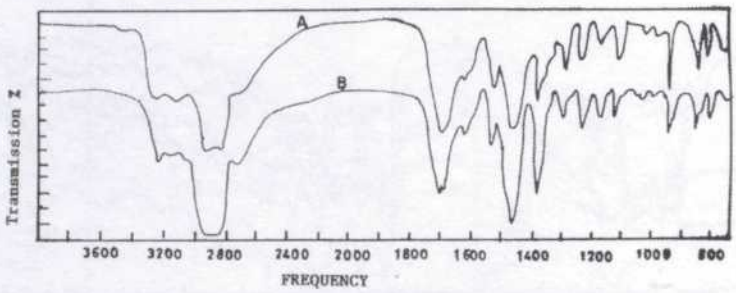


Fig. 7: IR-absorption spectra of 2–amino–4–hydroxy–6–methyl pteridine (10)
A: Natural B: Synthetic

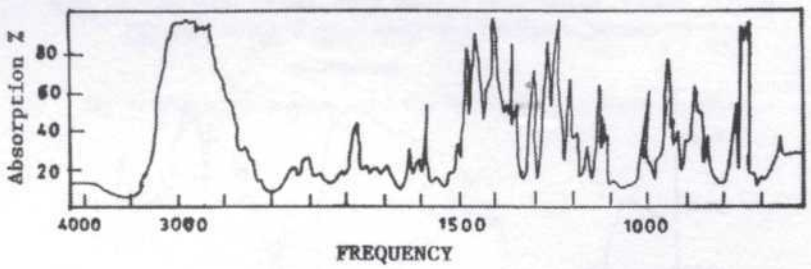


Fig. 8: IR-absorption spectra of Benzimidazole (7)

TABLE 1
IR absorption bands and melting point of 2, 6-diamino-8-chloroalkyl purines (3000-4000cm^{-1})

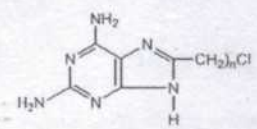
n	IR cm-1 (KBr)	m.p
1	3415, 3337, 3269, 3154, 3020 – NH2,-NH	300^{0}C
2	3400, 3344, 3202, 3147 – NH2,-NH	300^{0}C

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

n	IR cm –1 (KBr)	m.p
1	- - -	- - -
2	3464, 3450,3339, 3281, 3125, - OH, -NH2, - NH	300 C
3	3450, 3393, 3380, 3374, 3168, 3006 -OH, -NH2, -NH	300 C

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

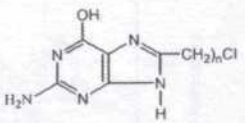
A



cont. TABLE 3

n	IR cm-1 KBr
1	2971, 2809, 1647, 1618, 1590, 1569, 1520, 1492, 1449, 1435, 1400, 1315, 1259, 1238, 175, 1020, 981, 963, 780, 710, 639
2	2956, 2886, 2745, 2661, 1660, 1618, 1561, 1498, 1449, 1399, 1378, 1308, 1272, 1202, 1160, 1019, 984, 934, 892, 786, 709, 666
3	2985, 2942, 2921, 2816, 1646, 1611, 1561, 1498, 1449, 1371, 1285, 1209, 1174, 1146, 1089, 1005, 984, 927, 899, 843, 786, 666

B



n	IR cm-1 KBr
1	2971, 2928, (-CH_2-),1681, 1632, 1575, 1484, 1449, 1406, 1315, 1237, 1216, 1153, 1012, 927, 892, 772, 702, (-CH_2Cl), 652
2	2971, 2935, (CH2-), 1681, 1632, 1575, 1484, 1449, 1408, 1348, 1300, 1237, 1209, 1106, 1012, 989, 778, 695, (-CH_2Cl), 652

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 90.1 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 seriesw 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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