Characterization and biological studies of bis- and tera-acetyl derivatives of hydrocarbon-bridged Diamines-I

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Abstract: A systematic study of the pharmaceutically important, double ended, chelating agents of the types $CH_3CONH(CH_2)_nNHCOCH_3$ and $(CH_3CO)_2N(CH_2)_n\ N(COCH_3)_2$, where n= 2, 3, 4, 5 and 6, prepared by the bis- and tetra-acetylation of the corresponding diamino-polymethylenes, have been carried out. Bis- and tertra-acetyl derivatives have been characterized by their elemental analysis and the FTIR spectra, Mass spectra and H-NMR spectra of these compounds have been reported to establish their structures. In the present work, FTIR spectra have been found an excellent means for distinguishing the bis-acetyl derivatives from their tetra-acetyl counterparts. The structures of these bis- and tetra-acetyl compounds have further been established by their H-NMR and Mass Spectra. The selective pharmacological screening of the derivatives was carried out according to the standard procedures. The compounds were screened for their antibacterial and antifungal activities and it was found that majority of these compounds did not possess any remarkable activity. Only the compound BA1,2-DAE, showed significant antifungal activity against *Microsporum canis* (80 %).

Keywords: Acetylation, double-ended chelating compounds, tetra-acetyl derivatives, antibacterial activity

INTRODUCTION

Acetylation describes a reaction that introduces acetyl functional group (CH_3CO), into an organic compound, by replacing active hydrogen atom(s). Commonly acetylation is carried out by using acetic anhydride or acetyl chloride and amino or hydroxyl functional groups present in the compounds are acetylated. The role of acetylation in drug synthesis has long been recognized and a number of different Active Pharmaceutical Ingredients (APIs) and therapeutically important drug candidates are being synthesized by the process of acetylation. The acetylation of an amino group is an important fundamental transformation in pharmaceutical chemistry (Greene and Wuts, 1999; Pearson and Roush, 1999) and this transformation leads to the development of new pharmaceutically active compounds. Some of the derivatives synthesized by the acetylation of amino group containing compounds, being presently marketed in different pharmaceutical preparations include acetyl cysteine, acetaminophen and phenacetin (Gerbino, 2005; Hoover, 1975).

The, double-ended chelating compounds, synthesized by the acetylation of diamines, have previously been reported to be very effective for cancer chemotherapy, due to their chelating effect with the substrate (Breslow *et al*., 2000; Gershell, 2001). This approach of inducing chelating effect was successfully invoked by linking two amide groups together through linker polymethylene groups of varying length chains and designing the compounds more effective at differentiating murine erythroleukemia cells (Grainger *et al*., 1992; Reuben *et al*., 1978; Reuben *et al*., 1976 and Tanaka *et al*., 1975).

Although, the crystal structure studies of many of these compounds have previously been reported (Aakeröy *et al*., 2010; Zhang *et al*., 1996) and in some cases these compounds have been used in the synthesis of their metal complexes (Chatterton *et al*., 2001, Goodgame *et al*., 2000; Goodgame *et al*., 1999; Hussain, 2007; Hussain and Goodgame, 2007) but no systematic studies for the characterization of these compounds have been carried out and no report on the antibacterial and antifungal studies of these compounds exists.

Keeping in view the pharmaceutical and biological effectiveness of the double-ended chelating ligands, we decided to carry out a systematic study of two possible series of hydrocarbon chain linked bis-acetyl and tetra-acetyl compounds and established their structures by their elemental analysis and by measuring their FTIR spectra, Mass spectra and H-NMR spectra. Further, the reported pharmacological screening of the compounds, studied in the present work, was carried out as per standard procedures. The screening of the compounds was carried out for their antibacterial and antifungal activities.

MATERIALS AND METHODS

Chemicals and equipments

All the chemicals used in the present work were of reagent grade and were used without further purification. FTIR spectra (4000-400 cm^{-1}) were obtained by using

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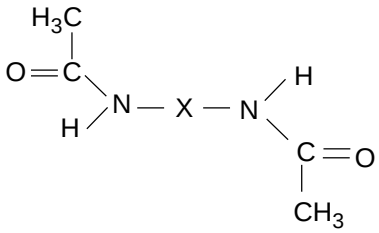
Perkin-Elmer 1720 FTIR spectrometer, H-NMR spectra were recorded on Brucker AM-300/AM400 and Mass spectra were measured on MAT-312 or JEOL, IMS-HX 110 instruments.

Preparation of bis-acetyl diamino derivatives

All the bis-acetyl diamino compounds in the present work were synthesized by previously reported methods (Grainger *et al*., 1992; Reuben *et al*., 1978; Reuben *et al*., 1976; Tanaka *et al*., 1975, Goodgame *et al*., 1999), by reacting the appropriate diamino alkane and acetic anhydride in 1:2 ratio and heating the resulting solution for varying lengths of time. The bis-acetyl derivatives thus formed were recrystallised and dried in vacuo. The following bisacetyl derivatives were prepared, the elemental analysis data of which is listed in table 2.



Where X = $(CH_2)_2$, $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_6$. NMR (ppm) results of N,N′-bis-acetyl 1,2-diaminoethane (BA 1,2-DAE): 1.9 (s, **6H**, CH_3-H), 3.2 (s, **4H**, CH_2-H), 6.4 (m, **2H, N**H_2-H).

NMR (ppm) results of N,N′-bis-acetyl 1,3-diaminopropane (BA 1,3-DAP): 1.5 (m, **2H**, CH_2-H), 1.9 (s, **6H**, CH_3-H), 3.2 (s, **4H**, CH_2-H), 6.7 (m, **2H, N**H_2-H).

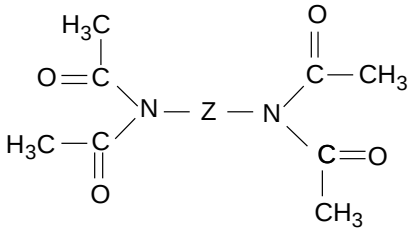
NMR (ppm) results of N,N′-bis-acetyl 1,4-diaminobutane (BA 1,4-DAB): 1.5 (m, **4H**, CH_2-H), 2.0 (s, **6H**, CH_3-H), 3.2 (s, **4H**, CH_2-H), 5.8 (m, **2H, N**H_2-H).

NMR (ppm) results of N,N′-bis-acetyl 1,5-diaminopentane (BA 1,5-DAPen): 1.3 (w, **2H**, CH_2-H), 1.5 (m, **4H**, CH_2-H), 1.9 (s, **6H**, CH_3-H), 3.2 (m, **4H**, CH_2-H), 5.7 (w, **2H, N**H_2-H).

NMR (ppm) results of N,N′-bis-acetyl 1,6-diaminohexane (BA 1,6-DAH): 1.3 (s, **4H**, CH_2-H), 1.47 (m, **4H**, CH_2-H), 1.97 (s, **6H**, CH_3-H), 3.2 (s, **4H**, CH_2-H), 5.5 (w, **2H, N**H_2-H).

Preparation of tetra-acetyl diamino derivatives

All the tetra–actyl diamino derivatives were synthesized by previously reported methods (Aakeröy *et al*., 2010; Zhang *et al*., 1996; Goodgame *et al*., 2000), by reacting the relative diamino alkanes with acetic anhydride in the ratio of 1:4 and refluxing the resulting solution for 20-24 hours. The tetra-acetyl compounds formed were recrystallised and dried in the vacuo. The following tetraacetyl derivatives were prepared, the elemental analysis data of which is listed in table 2.



Where Z = $(CH_2)_2$, $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_6$. NMR (ppm) results of N, N, N′, N′-tetra-acetyl 1,2-diaminoethane (TA 1,2-DAE): 2.2 (vs, **12H**, CH_3-H), 3.6 (m, **4H**, CH_2-H).

NMR (ppm) results of N, N, N′, N′-tetra-acetyl 1,3-diaminopropane (TA 1,3-DAP): 1.7 (m, **2H**, CH_2-H), 2.2 (vs, **12H**, CH_3-H), 3.6 (s, **4H**, CH_2-H).

NMR (ppm) results of N, N, N′, N′-tetra-acetyl 1,4-diaminobutane (TA 1,4-DAB): 1.55 (m, **4H**, CH_2-H), 2.4 (vs, **12H**, CH_3-H), 3.6 (s, **4H**, CH_2-H).

NMR (ppm) results of N, N, N′, N′-tetra-acetyl 1,5-diaminopentane (TA 1,5-DAPen): 1.2 (w, **2H**, CH_2-H), 1.5 (m, **4H**, CH_2-H), 2.2 (s, **6H**, CH_3-H), 3.5 (m, **4H**, CH_2-H).

NMR (ppm) results of N, N, N′, N′-tetra-acetyl 1,6-diaminohexane (TA 1,6-DAH): 1.3 (m, 4**H**, CH_2-H), 1.5 (m, **4H**, CH_2-H), 2.4 (s, **12H**, CH_3-H), 3.6 (m, **4H**, CH_2-H).

Preparation of standard indicator microorganisms for antimicrobial screening

The standard indicator microorganisms, desired during the present study, for antibacterial and antifungal screening were prepared by the method of Moshafi *et al*., 2011.

Determination of Antibacterial activity

For antibacterial activity, the method used by Saify *et al* (2005) for the study of antibacterial activity of synthesized compounds during the present study was used.

Determination of antifungal activity

The compounds were tested for antifungal activity by Agar tube dilution method (Atta-ur-Rehman *et al*., 2001) using methanol as solvent.

For the fungicidal bioassay the test sample was dissolved in sterile DMSO to serve as stock solution. The sabouraud dextrose agar media was prepared by mixing sabouraud 4% glucose agar and dissolving it in distilled water and known amount dispensed in screw cap test tubes. The

non solidified sabouraud dextrose agar media was poisoned/ inoculated with the compound of desired concentration prepared from the stock solution. Each tube was inoculated with a 4 mm diameter disk of inoculums removed from seven days old culture of different fungi. For non-mycelial growth, an agar surface streak was employed. Other media were supplemented with DMSO and reference (standard) antifungal drugs i.e. Ketocanazole, Miconazole and Amphotericin serving as negative and positive control respectively.

Procedure was replicated three times and the tubes incubated in a slanting position at 27-30^{o}C for growth for 7-10 days. Growth on the compounds containing media was determined by measuring the linear growth (mm) and the inhibition in growth was calculated with reference to negative control. The test tube with no visible growth of the micro organisms was taken to represent the minimum inhibition concentration (MIC) of the test sample which is expressed in µg/mL. Growth inhibition was calculated with reference to positive control.

RESULTS

The melting points and the percentage yields of all the bis-acetyl and tetra-acetyl derivatives prepared for the present study are reported in table 1.

FTIR spectra of compounds

The FTIR spectra of the bis- and tetra-acetyl derivatives

Table 1: Physical Data of the Bis-acetyl and Tetra-acetyl derivatives.

Compounds	X	Formula	Melting Point	Percentage Yield
BA1,2-DAE	$(CH_2)_2$	$C_6H_{12}N_2O_2$	174-176 °C	66%
TA1,2-DAE	$(CH_2)_2$	$C_{10}H_{16}N_2O_4$	154-156 °C	56%
BA1,3-DAP	$(CH_2)_3$	$C_7H_{14}N_2O_2$	94	65%
TA 1,3-DAP	$(CH_2)_3$	$C_{11}H_{18}N_2O_4$	*	65%
BA1,4-DAB	$(CH_2)_4$	$C_8H_{16}N_2O_2$	138-140°C	75%
TA1,4-DAB	$(CH_2)_4$	$C_{12}H_{20}N_2O_4$	120-121 °C	82%
BA1,5-DAPen	$(CH_2)_5$	$C_9H_{18}N_2O_2$	*	68%
TA 1,5-DAPen	$(CH_2)_5$	$C_{13}H_{22}N_2O_4$	*	68%
BA1,6-DAH	$(CH_2)_6$	$C_{10}H_{20}N_2O_2$	127-129 °C	72%
TA1,6-DAH	$(CH_2)_6$	$C_{14}H_{24}N_2O_4$	45-46 °C	61%

* Liquid, the B.P. was not determined.

Table 2: Characteristic IR Spectral Bands and Analytical Data of the Bis-acetyl and Tetra-acetyl derivatives

Compound	N-H Stretch	C=O Stretch	Amide II Band	C-N Stretch	Analytical Data		
					% C	% H	%N
BA 1,2-DAE	3296 VS, B	1652 VS, B	1563 VS, B	---	50.75 (50)	8.45 (8.33)	19.50 (19.44)
TA 1,2-DAE	---	1707 VS, Br	---	1356 VS	51.75 (52.63)	7.01 (7.03)	12.28 (12.44)
BA 1,3-DAP	3273 VS	1626 VS	1549 VS	---	52.90 (53.16)	8.75 (8.86)	17.68 (17.72)
TA 1,3-DAP	---	1686 S	---	1367 VS	53.16 (54.54)	7.22 (7.43)	11.72 (11.57)
BA 1,4-DAB	3299 VS	1634 VS, B	1541VS,B	---	55.93 (55.81)	9.43 (9.30)	16.33 (16.27)
TA 1,4-DAB	---.	1711, 1684 VS	---	1366 S	56.13 (56.25)	7.83 (7.81)	10.83 (10.93)
BA 1,5-DAPen	3285 S	1626 VS	1552 VS	---	58.76 (58.06)	9.06 (9.67)	14.45 (15.05)
TA1,5-DAPen	---	1685 VS	---	1367 VS	57.06 (57.77)	8.65 (8.14)	10.97 (10.37)
BA 1,6-DAH	3305VS,B	1630VS	1538 S	---	60.80 (60.00)	10.15 (10.00)	14.25 (14.00)
TA 1,6-DAH	---	1688 VS	---	1348 VS	59.10 (59.15)	8.55 (8.45)	9.95 (9.85)

have been measured in the range 4000-600 cm^{-1} and the characteristic IR spectral bands, together with their elemental analysis data, are listed in table 2. In the IR spectra of all the bis-acetyl derivatives, due to the presence of amide group, the N-H stretching absorption appeared near 3300 cm^{-1}, whereas in the spectra of tetra-acetyl derivatives this band did not appear due to the absence of N-H group (table 2). Further, the carbonyl stretching band in bis-acetyl derivatives appeared around 1630 cm^{-1} whereas in tetra-acetyl derivatives this band appeared close to 1690 cm^{-1}. In the FTIR spectra of bis-acetyl derivatives, amide II band appeared near 1540 cm^{-1} whereas due to the absence of amide group in tetra-acetyl derivatives this band could not be seen in their IR spectra. However, in the spectra of tetraacetyl compounds C-N stretching band appeared near 1365 cm^{-1}, as can be seen in figs. 1-2.

Mass spectra of compounds

The mass spectra of all the N,N,N',N'-tetra-acetyl diamino derivatives, studied in the present work, were measured by using FAB positive technique of ionization.

In the mass spectrum of N,N,N',N'-tetra-acetyl 1,2-diaminoethane the appearance of highest peak at m/e 229, confirmed the formation of tetraacetyl derivative as shown in fig. 3.

The appearance of next peak at m/e 187, suggested the replacement of one acetyl group by a hydrogen atom, resulting in the formation of N,N,N'-triacetyl 1,2-diaminoethane molecular ion. Subsequent elimination of another acetyl fragment, resulted in the formation of N, N'-bisacetyl 1,2-diaminoethane molecular ion (m/e 145) as shown in Scheme I.

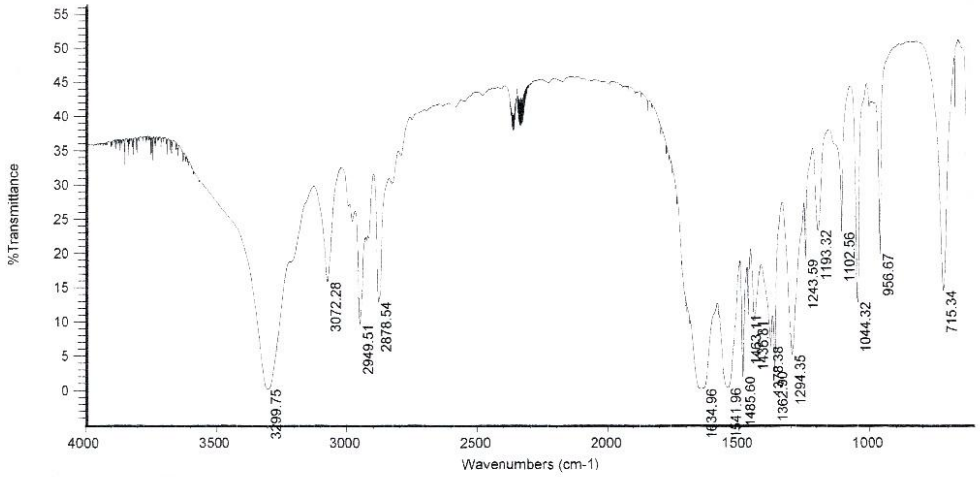


Fig. 1: FTIR Spectrum of Bisacetyl 1,4-diaminobutane

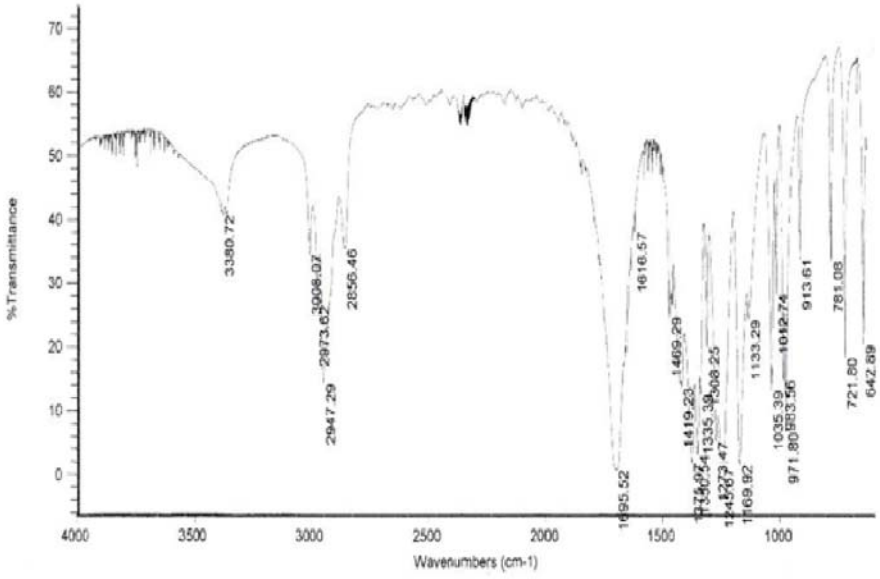


Fig. 2: FTIR Spectrum of Tetraacetyl 1,6-diaminohexane

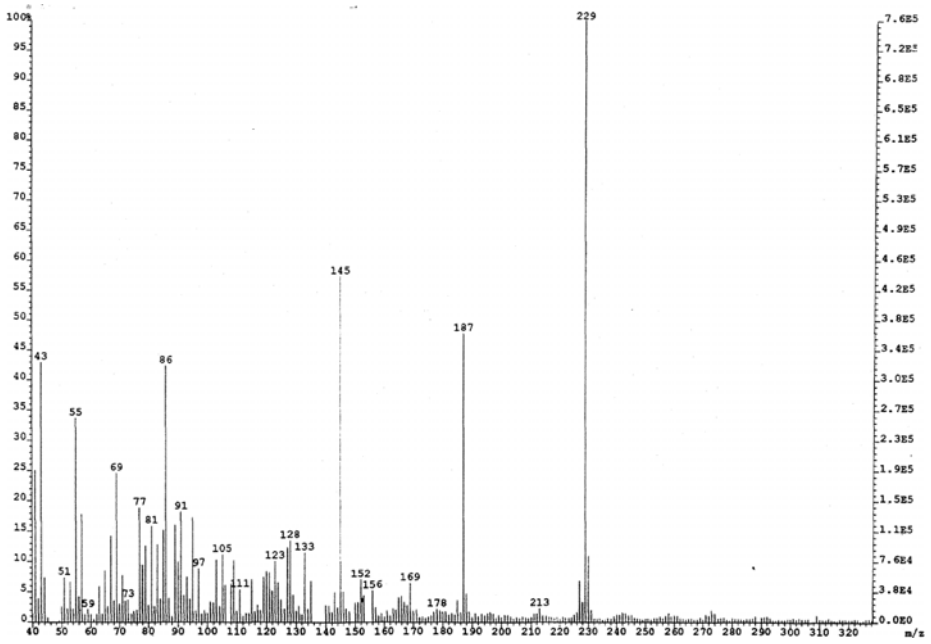
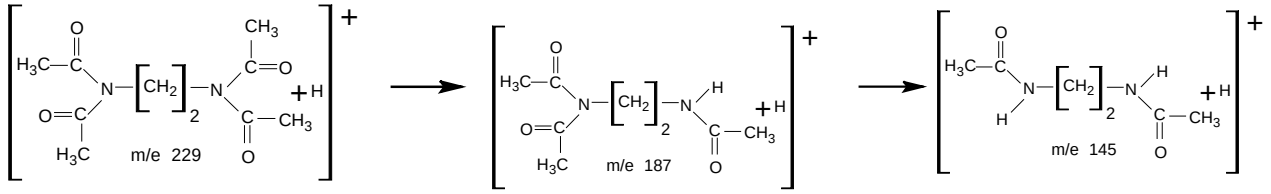


Fig. 3: Mass Spectrum of Tetraacetyl 1,2-diaminoethane



Scheme I: Fragmentation pattern of N,N,N',N'-tetraacetyl 1,2-diaminoethane

H-NMR Spectra of compounds

The proton Nuclear Magnetic Resonance (H-NMR) spectra of all the bis- and tetra-acetyl compounds, prepared in the present study, were measured. In the H-NMR spectra of all N, N′-bis-acetyl diamino derivatives, a sharp singlet due to 6 identical protons, from two methyl groups, appeared around 2.0 ppm. A broad peak, due to 2 protons from N-H groups was observed around 6 ppm in NMR spectra of all bis-acetyl derivatives as shown in figs. 4-5.

The NMR spectra of all N, N, N′, N″-tetra-acetyl diamino derivates exhibited a sharp peak of 12 protons, as singlet, which appeared due to the presence of four identical CH_3 groups, in each of these compounds. Further, due to absence of N-H group in all these tetraacetyl derivatives, no broad peak, around 6 ppm, could be seen in their NMR spectra as shown in fig. 6.

Antimicrobial screening of compounds

For bactericidal activity, the compounds were screened against six pathogenic micro organisms. Among them two were Gram-positive and four were Gram-negative.

The Gram-positive bacteria included *staphylococcus aureus* and *Bacillus subtilus*, whereas Gram-negative included *Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi* and *Shigella flexneri*. Activity was reported in terms of zone of inhibition in millimeters. Antibacterial effects were compared with the standard drug Imipenum.

For fungicidal activity the compounds were screened against six micro organisms. They included three human pathogens i.e. *Trichphyton longifusus*, *Candida albicans, Aspergillus flavus*, two plant pathogens i.e. *Fusarium solani, Candida glabarata* and one animal pathogen which was *Microsoprium canis*. Growth inhibition was calculated with reference to positive control and was taken as 200 mg/ml for the sample. Miconazole was used as standard reference drug.

DISCUSSIONS

Among the bis-acetyl derivatives, bis-acetyl diaminopentane has the lowest melting point, whereas, among the tetra-acetyl derivatives, tetra-acetyl diamino-propane and tetra-acetyl diaminopentane, have the lowest

melting points and all these three compounds exist in liquid state at room temperature.

In the FTIR spectra, the criterion for the formation of bis- and tetra-acetyl compounds is the appearance of N-H stretching band near 3300 cm^{-1}, carbonyl stretching band

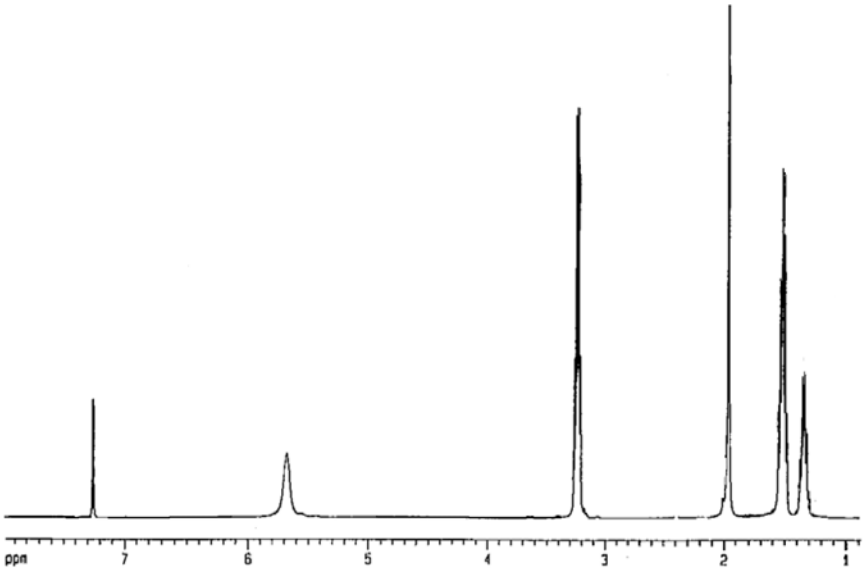


Fig. 4: NMR Spectrum of Bisacetyl 1,5-diaminopentane

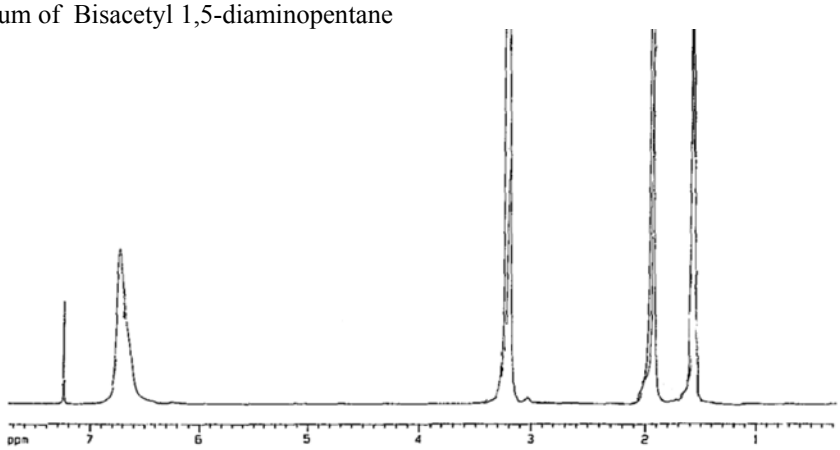


Fig. 5: NMR Spectrum of Bisacetyl 1,3-diamino propane

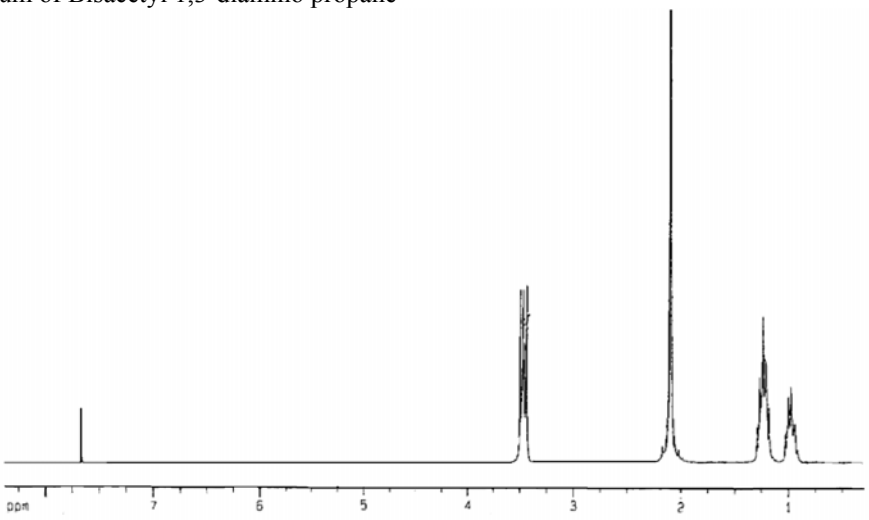


Fig. 6: H-NMR Spectrum of Tetra acetyl 1,5-diaminopentane

around 1630 cm^{-1} and amide II band close to 1540 cm^{-1} in the spectra of bis-acetyl compounds and the appearance of only carbonyl stretching frequency around 1700 cm^{-1} in the IR spectra of tetra-acetyl derivatives. In the FTIR spectra of all these compounds the same criterion was found to be observed completely.

The mass spectra of all the compounds, synthesized in the present work, showed the same fragmentation pattern as observed in the case of N,N,N',N'-tetra-acetyl 1,2-diaminoethane reported above. The highest peak in the Mass spectra of all these compounds was observed at m/e ratio, which corresponded to their molecular masses, with one additional proton and confirmed the formation of tetraacetyl derivatives. The next lower peak appeared in the mass spectra of all these compounds, at the m/e ratio, which corresponded with the replacement of one acetyl group by a proton. The third peak in their mass spectra appeared at m/e ratio which corresponded to the replacement of two acetyl groups by two protons and resulted in the formation of corresponding N, N'-bisacetyl derivatives.

The NMR peaks due to hydrogen atoms of methyl groups, NH groups and methylene groups of spacer chain, in all the bis-acetyl derivatives, matched very well with the expected peak positions and confirmed the structures of these compounds. Like their bis-acetyl counterparts, in the H-NMR spectra of all the tetra-acetyl derivatives, the signals due to hydrogen atoms of methyl groups and methylene groups of spacer chain, matched very well with the expected peak positions and confirmed the structures of these tetra-acetyl compounds.

From the bactericidal activity data collected during the present work, it was observed that these compounds did not possess any remarkable bactericidal activity against any bacterial strain mentioned above. The sample TA 1,2-DAE had shown non-significant activity against *shigella flexneri* (10 mm) and the compound TA1,4-DAB had exhibited low antibacterial activity against *shigella flexneri* (14 mm).

The results of fungicidal bioassay show that only the first compound of the series i.e. BA 1,2-DAE, showed significant activity against *Microsporum canis* (80 %). All the remaining compounds either did not exhibit any activity at all or showed to have low activity against the above named microorganisms. The compound TA 1,4-DAB exhibited non-significant activity against *Microsporum canis* (20 %) and against *Fusarium solani* (20 %) and the compound TA 1,6-DAH exhibited non significant activity against *Microsporum Canis* (20%).

CONCLUSION

In the present work, the structures of pharmaceutically important, double ended, chelating agents of the types $CH_3CONH(CH_2)_nNHCOCH_3$ and $(CH_3CO)_2N(CH_2)_nN(COCH_3)_2$, where n=2, 3, 4, 5 and 6, have been established by their elemental analysis, FTIR spectra, H-NMR and Mass Spectra. Further, FTIR spectroscopy has been found an excellent technique for distinguishing the bis-acetyl derivatives from their tetra-acetyl counterparts. The selective pharmacological screening of these derivatives suggest that majority of these compounds did not exhibit any remarkable antibacterial and antifungal activity. Only the compound BA1,2-DAE showed significant antifungal activity against *Microsporum canis* (80%).

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