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Original Research Article

Investigation of dibromo and N-bromoacetyl derivatives of [b] carbazole-synthesis and antibacterial evaluation

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ABSTRACT

The synthesis, structure and biological activity of carbazole compounds has been long focus of research interests in the field of medicinal chemistry. 5,8-dibromo-5,6-dihydro(3,2-a) carbazole A have prepared in good yield by a free radical bromination reaction of 8-bromo-5,6-dihydro9(3,2-a)carbazole with N-bromosuccinimide in carbontetrachloride at ambient temperature. Compound 2 have prepared by free radical brimination method in carbontetrachloride at 40°C. Synthesis of compound C have carried out by free radical bromination with 5-bromo-1,2,3,4-tetrahydrocyclopenta(b)indole as reactant, in dichloromethane at ambient temperature. Compound 2, 4, and 6 were synthesized by N-bromoacetylation method using bromoacetylbromide as reactant. All the synthesized compounds were characterized and confirmed by various instrumental techniques Viz, UV-visible, FTIR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy. All the synthesized compounds were subjected to the antibacterial evaluation with standard Ciprofloxacin. The results showed that the synthesized compounds exhibit excellent antibacterial activity.

Keywords: N-bromosuccinimide, bromoacetylbromide, carbontetrachloride, N-bromoacetyl-5,8-dibromo-5,6-dihydro[3,2-a]carbazole.

1. INTRODUCTION

Nitrogen-containing heterocycles (N-heterocycles) have tremendous applications in pharmaceutical and material sciences.[1] Heterocyclic compounds are acquiring more importance in recent years because of their broad pharmacological activities. Nitrogen, sulphur or oxygen containing five or six member heterocyclic compound has occupied enormous significance in the field of medicinal chemistry. Indoles are an important class of heterocycles not only ubiquitous compounds in nature but also because they have a wide range of biological activities. The indole moiety is found in various pharmacologically and biologically active compounds [2]. Indole is the most beneficial heterocyclic nucleus which has gained prominence in medicinal chemistry due to its diverse biological activities such as anticonvulsant [3-8], anti-inflammatory [9] and antipsychotic [10] activities. Heterocyclic ring system of tetrahydrocarbazole and their derivatives are used with great interest for the past and recent years due to wide variety of biological application such as antimicrobial activity [11], anticancer & antitubercular [12] and anticonvulsant [13] activities.

Bromination is a very important process in organic synthesis as bromo derivatives serve as useful intermediates in the manufacture of pharmaceuticals, agrochemical and other specialised chemicals. [14,15] Moreover, many pesticides, insecticides, herbicides and fire retardants contain the bromine functionality. [16,17] *N*-Bromosuccinimide is one of the most pronozing brominating agents, especially for free radical bromination. The aim of present study is to develop novel, efficient, convenient and selective synthetic methods in organic chemistry, which helps the drug discovery and medicinal chemistry.

2. EXPERIMENTAL SECTION

2.1. Methods and materials

All the chemicals used were purchased from Merck and Aldrich and used without further purification.

The melting points of synthesized compounds were determined by open capillary tubes using an X-5A Melting point apparatus and were uncorrected. Thin layer chromatography among to most useful tools for following the progress of organic chemical reaction and for assaying the purity of organic compounds. FTIR spectra was recorded on a Alpha Bruker FTIR Spectrometer using KBr pellets. The ^{1}H NMR Spectra were measured on a Bruker proton NMR-Avance 400 MHz with chemical shift expressed in ppm downlfield from TMS as internal standard in DMSO(d-6). The ^{13}C NMR Spectra were determined at 400 MHz with a Bruker Avance Spectrometer. Mass Spectra were recorded on GC-MASS Spectrometer using methanol as a solvent.

Synthesis and characterisation of 5,8-dibromo-5,6-dihydro[3,2-a]carbazole, 2,6-dibromo-12,34-tetrahydrocarbazole and 2,5-dibromo-1,2,3,4-tetrahydrocyclopenta[b]indole have been carried out according to the literature Guhanathan *et al* 2018.

2.2. Synthesis of N-bromoacetyl-5,8-dibromo-5,6-dihydro[3,2-a]carbazole

A mixture 5,8-dibromo-5,6-dihydro[3,2-a]carbazole (0.7540g, 0.0020mole), bromoacetyl bromide(0.4037g, 0.0020mole) and 20ml of dry DMF was stirred at 70°C for 2 hours. After completion of reaction with found using TLC , the reaction mixture was poured into ice-cold water. The crude product was filtered and the precipitate was washed with water. Dried the precipitate and recrystallized with hot ethanol, to afford compound **i**n a good yield.

Yield: 80%, Melting point 86-90℃, FTIR(KBr): =C-H-3051cm^{-1},-C-H-2854cm^{-1} ,C=O-1705cm^{-1} ,C=C-1458cm^{-1}. ^{1}H NMR (DMSO d_6): 8.731-8.765 ppm (H, **d**) ,8.518-8.589(H, **d**), 7.639-8.4(4H ,m), $COCH_2$ (3.33ppm , **s**), Aliphatic protons 0.849-2.892ppm. ^{13}C NMR(DMSO d_6): 122-126, 79.44. Mass spectrum: m/e ratio 500 (M+2).

2.3. Synthesis of N-bromoaceztyl-2,6-dibromo-1,2,3,4-tetrahydrocarbazole

N-bromoaceztyl-2,6-dibromo-1,2,3,4-tetrahydrocarbazole was synthesized by Scheme-2, 2,6-dibromo-1,2,3,4-tetrahydrocarbazole (0.7239g, 0.0022mole) and bromoacetyl bromide (0.4406g, 0.4406mole) were dissolved in 20ml of dry DMF and the reaction mixture was allowed reflux at 70°C with constant stirring about 2 hours, simultaneously the reaction progress was monitored by TLC. After completion of the reaction, the mixture was poured into crushed ice. Filtered the precipitate and washed the precipitate with water and dried. The crude product was recrystallized with hot ethanol which yield the pure product.

Yield:85% , Melting point 122-124℃, FTIR(KBr): =C-H-2927cm^{-1} ,-C-H-2848cm^{-1} , C=O-1707cm^{-1}. ^{1}H NMR (DMSO d_6): 1.708-1.825(4H , **m**), 1.875-1.924(2H**, t**) , 3.446(2H , **s)**, 1.948-1.959(2H , **d)**, 2.204-2.273(H, **m**), 7.272-7.293(2H**, d**) ,8.936, 9.640(H, **s)**. ^{13}C NMR (DMSO d_6): 122-126, 79 & 20. Mass spectrum : m/e ratio 446(M+).

2.4. Synthesis of N-bromoacetyl-2,5-dibromo-1,2,3,4 tetrahydrocyclopenta[b]indole

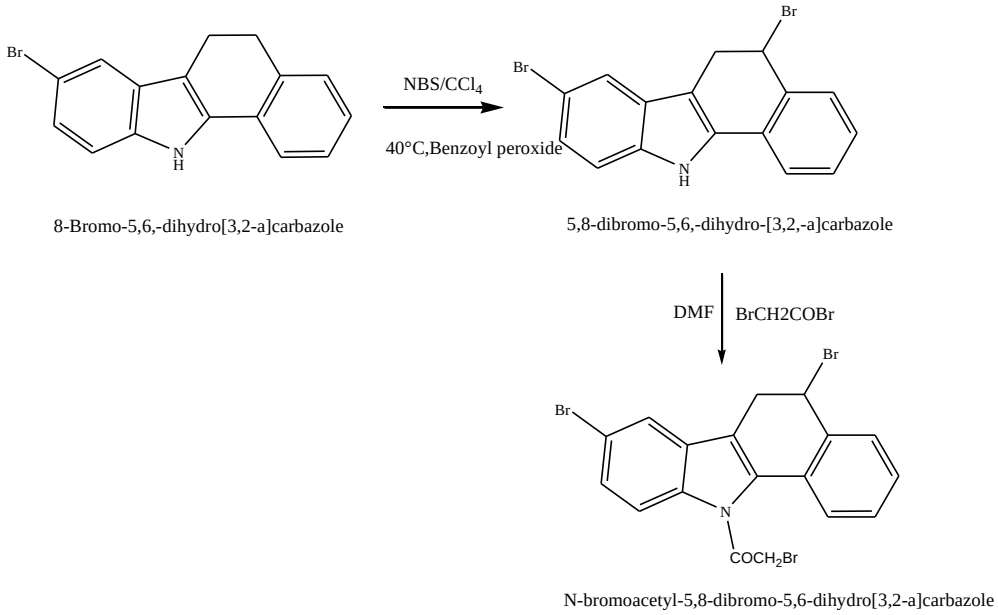
2,5-dibromo-1,2,3,4-tetrahydrocarbazolecyclopenta[b]indole **(**0.732g, 0.002mole) and bromoacetylbromide (4g) in 20ml of dry DMF taken in a round bottom flask fitted with a condenser were heated to reflux at 70°C with continuous stirring for 2hours. The reaction progress was monitored by TLC , then the reaction mixture was put into ice-cold water. The obtained precipitate was filtered and washed with water and allowed to dried. The dried precipitate was recrystallized with hot ethanol in order to obtain the pure compound .

Yield :85-90% , Melting point 144-116 ℃, FTIR(KBr): =C-H-2920 cm^{-1} ,-C-H-2854 cm^{-1},C=O-1653 cm^{-1} ,C=C-1463 cm^{-1} ,C-Br- 805 cm^{-1} . ^{1}H NMR (DMSO d_6): 1.876-2.055(2H, **m)** ,2.107-2.109(H, **d)** ,$COCH_2$ (3.471, **s)** ,6.688-6.690(H **, d**) , 7.181-7.200(H**, d**) ,7.654(H, **s**). ^{13}C NMR(DMSO d_6): 129-136, 29 & 20. Mass spectrum : m/e ratio 436 (M+1).

2.5. Bacterial cultures and evaluation of antimicrobial activities

2.5.1. Agar well diffusion method

Antimicrobial analysis was followed using standard agar well diffusion method to study the antibacterial activity of compounds (Perez *et al*., 1990; Erdemoglu *et al*., 2003; Bagamboula *et al*., 2004). Each bacterial isolate was suspended in Brain Heart Infusion (BHI) broth and diluted to approximately 10^5 colony forming unit (CFU) per ml. The test organisms were flood-inoculated onto the surface of BHI agar and then dried. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer and 30µL (50µg compound in 1 ml of solvent-Ethanol) of the sample solution were poured into the wells. The plates were incubated for 18 hours at 37ºC for bacteria. Antibacterial activity was evaluated by measuring the diameter of the zone inhibition in mm against the test microorganisms. DMSO was used as solvent control. Ciprofloxacin was used as reference antibacterial agent. The tests were carried out in triplicate.

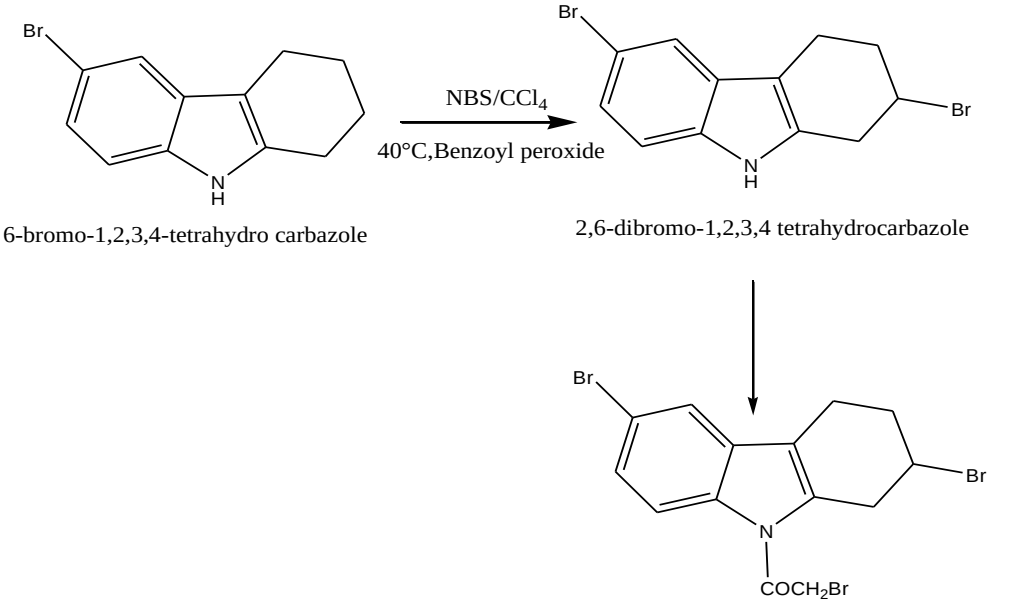


8-Bromo-5,6,-dihydro[3,2-a]carbazole

5,8-dibromo-5,6,-dihydro-[3,2,-a]carbazole

N-bromoacetyl-5,8-dibromo-5,6-dihydro[3,2-a]carbazole

SCHEME 1. Synthesis of N-bromoacetyl- 5,8-dibromo5,6-dihydro(3,2-a)carbazole

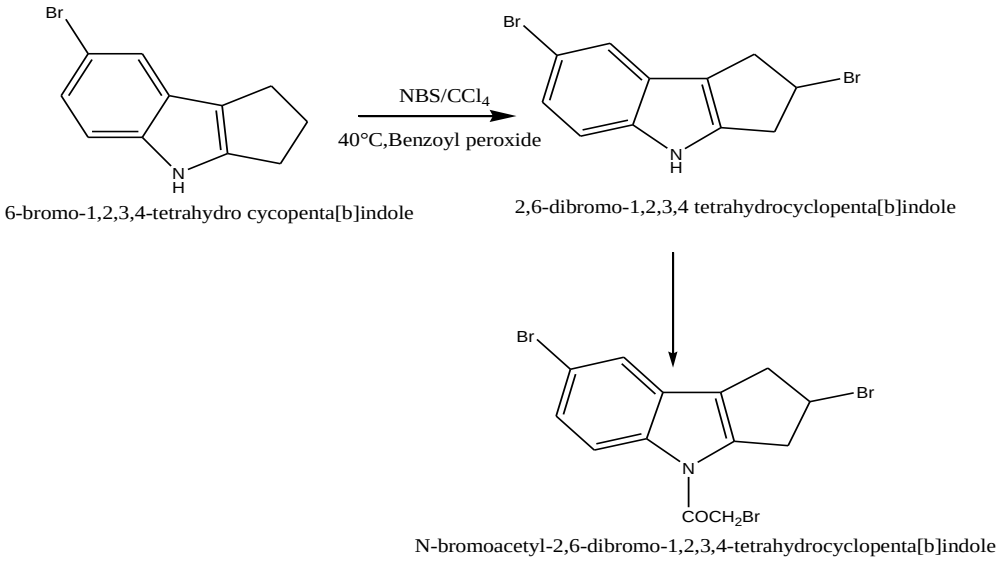


6-bromo-1,2,3,4-tetrahydro carbazole

2,6-dibromo-1,2,3,4 tetrahydrocarbazole

N-bromoacetyl-2,6-dibromo-1,2,3,4-tetrahydrocarbazole

SCHEME 2. Synthesis of N-bromoacetyl-2,6-dibromo-1,2,3,4-tetrahydrocarbazole



6-bromo-1,2,3,4-tetrahydro cycopenta[b]indole

2,6-dibromo-1,2,3,4 tetrahydrocyclopenta[b]indole

N-bromoacetyl-2,6-dibromo-1,2,3,4-tetrahydrocyclopenta[b]indole

SCHEME 3. Synthesis of N-boromoacetyl-2,6-dibromo—1,2,3,4-tetrahydrocyclopenta(b)indol

3. RESULT AND DISCUSSION

3.1. N-Bromoacetyl-5,8-dibromo-5,6-dihydro[3,2-a]carbazole

Figure 1 shows the obtained FTIR spectrum of compound 2. The band appears at 3051cm^{-1} and 2854 cm^{-1} have been assigned to aromatic C-H and aliphatic C-H stretching vibration. The medium peak at 1705cm^{-1} associated with C=O stretching vibration. The peak observed at 1458 cm^{-1} found to C=C stretching vibration. The band present at 800 cm^{-1} was observed due to C-Br stretching vibration. The ^{1}H spectrum of compound 2 have shown in Figure 2. The doublet appears at 8.731 ppm to 8.765 ppm corresponds to C-1 protons. The doublet signal appears at 8.518 ppm to 8.589 ppm corresponds to C-9 protons. A chemical shift at 8.498 ppm was attributed to the C-7 protons. The doublet peat appears at 8.258 ppm to 8.278 ppm corresponds to C-4 protons. A two doublet appears at 8.043 ppm to 8.237 ppm corresponds to C-3 protons. The doublet for C-2 protons appears at 7.639 ppm to 7.646 ppm. A singlet peak appears at 3.33 ppm was aattributed to the $COCH_2$ protons. The chemical shift at 2.503 ppm due to solvent DMSO(d-6). The triplet peak at 2.513 ppm to 2.892ppm corresponds to C-5 (CH-Br) protons. The doublet peak at 20.849 ppm to 1.215 ppm corresponds to C-6 protons.

The Figure **3** shows ^{13}C NMR spectra of the compound **2**. The peak appears at 29.44 ppm was attributed to the three aliphatic carbons denoted by C-5, C-6 & -CH_2Br (position 12). The

chemical shift value 112.52 ppm corresponds to C-14 proton. The carbon signal at 113.78 ppm due to the C-8 carbon. The the signal appears at 124.30 ppm corresponds to C-7 carbon atom. The chemical shift value 125.59 ppm was observed due to the C-9 carbon. The C-1 carbon corresponds to the signal appears at 126.14 ppm. The signal appears at 127.17 ppm describes the C-15 carbon. The peak appears at 127.24 ppm corresponds to C-3 carbon. The chemical shift value appears at 127.90 ppm which represent C-2 carbon. The C-13 carbon have shown the spectral value at 128.04 ppm. The signal appears at 132.68 ppm was due to C-16 carbon. The C-11 carbon shows the chemical shift value at 136.38 ppm. The signal appears at 137.93 ppm corresponds to C-17 carbon. The mass spectrum of the compound **2** has shown the molecular ion peak at m/z 500.6877 represented in Figure 4. Calculated value for compound 2 is 500.17 was good agreement with observed value.

3.2 N-bromoacetyl-2,6-dibromo-1,2,3,4- tetrahydrocarbazole

Figure 5 shows the FTIR Spectrum of N-Bromoacetyl-2,6-dibromo-1,2,3,4-tetrahydro carbazole. The band appears at 2927 cm^{-1} due to aromatic C-H stretching vibration. The band observed at 2848 cm^{-1} was found to aliphatic C-H stretching vibration. The medium band appears at 1707 cm^{-1}were assigned to C=O stretching vibration. The band present at 1462 cm^{-1} assigned to C=C stretching vibration. The medium band at 1274 cm^{-1} was observed due to C-N stretching vibration. The band appears at 464 cm^{-1} was found that C-Br stretching vibration.

Figure 6 shows the ^{1}H NMR spectrum of N-Bromoacetyl-2,6-dibromo-1,2,3,4-tetrahydro carbazole. The multiplet appears at 1.708 ppm to 1.825 ppm due to the C-3 protons. The two protons triplet appears at 1.875 ppm to 1.924 ppm represented by C-4 protons. A singlet appears at 3.446 ppm was denoted by C-9(CH2) protons. A doublet signal appeared at 1.948 ppm to 1.959 ppm was represented by C-1 proton, The multiplet signal appears at 2.204 ppm to 2.273 ppm due to C-2 protons (CH-Br). The doublet peak appears at 7.272 ppm to 7.293 ppm was designated by C-7 protons. A two singlet appears at 8.936 ppm to 9.640 ppm corresponds to C-4 & C-6 protons.

The ^{13}C NMR spectrum of N-Bromoacetyl-2,6-dibromo-1,2,3,4-tetrahydrocarbazole have shown in Figure **7**. The peak appears at 79.41 ppm corresponds due to the aliphatic carbon atoms

was denoted by C-1, C-2, C-3, C-4, & CH_2Br, The peak at 122.71 ppm corresponds to C-9 carbon. The chemical shift value appears at 123.57 ppm represent the C-5 & C-7 carbon. The spectral value at 124.67 ppm corresponds to C-9 carbon. The peak at 126.30 ppm due to the C-13 carbon atom. The CO peak observed at 190 ppm . The molecular ion peak of the compound **4** was observed m/z 446. Mass spectra of N-bromoacetyl -2,6-dibromo -1,2,3,4-tetrahydro carbazole have shown in Figure 8.

3.3 *N*-Bromoacetyl -2,5-dibromo-1,2,3,4-tetrahydrocyclopenta[b]indole

The FTIR spectrum of N-bromoacetyl-2,5-dibromo-1,2,3,4-tetrahydrocyclopenta[b]indole have shown in Figure **9**. The sharp band at 2920 cm^{-1} was observed due to the aromatic C-H stretching vibration. The band appears at 2854 cm^{-1} was associated the aliphatic C-H stretching vibration. The medium band at 1653 cm^{-1} were assigned due to the C=O stretching vibration. The peak at 1463 cm^{-1} was observed due to C=C stretching vibration. The band at 1294 cm^{-1} was associated with C-N stretching vibration. The medium band at 466 cm^{-1} were assigned to C-Br stretching vibration.

Figure 10 shows the ^1H NMR spectrum of compound 6. The multiplet at 1.876 ppm to 2.055 ppm corresponds to C-2(CH-Br) protons. A two doublet at 2.107 ppm to 2.109 ppm due to the C-1 & C-3 protons. A singlet at 3.471 ppm due to $COCH_2$ protons. The signal observed for one proton doublet at 6.688 ppm to 6.690 ppm was denoted by C-7 proton . A singlet at 7.654 ppm was due to C-4 protons. The doublet appears at 7.181ppm to 7.200 ppm due to C-6 protons.

Figure **11 shows ^{13}C NMR spectrum of compound 6.** The signals appears at 20.87 ppm due to the CH2Br. The chemical shift value appears at 29.14 ppm corresponds to aliphatic carbon denoted by C-1, C-2, & C-3 carbon atoms. The peak appears at 129.44 ppm corresponds to C-4 & C-6 carbon atoms. The chemical shift value appears at 139.79 ppm was described by C-5 carbon. The peak appears at 136.8 ppm indicates C-12 carbon.

The mass spectrum of the compound 6 has shown the molecular ion peak at m/z 436.4433 in Figure 12. The theoretical mass value of compound 6 was found m/z 435.94. This is good agreement with observed value.

3.4 Antibacterial activity

Antibacterial activity of various synthesized compounds

The results of antibacterial activity for synthesized compounds 2,4 &6 have shown in Table 1.The zone of inhibition was indicated the nature of antibacterial activity. The synthesized compounds were subjected to *staphylococcus aureas, streptococcus faecalis, Escherichia coli and salmonella typhi*. Compound 5 shows good antibacterial activity against *streptococcus faecalis, salmonella typhi* and *Escherichia coli.* Based on the survey of the antibacterial activity among the synthesized compounds 2, 4 &6 compound 4 found to have excellent activity 55% than the others.

Based on the literature survey cyclohexanone derivatives of carbazole found to have good antibacterial avtivity. Here in the carbazole synthesized from cyclohexanone would have been converted to bromination further conversion of N-acetylation. So, the N-acetylbromoderivative of carbazole (**4**) found to have excellent antibacterial activity 55% against all four i.e., two gram positive and two gram negative bacteria's.

4. CONCLUSION

The expected bromoderivative of carbazole compounds were synthesized by free radical bromination using 4-bromophenylhydrazine and various reactant such as alpha-tetralone, cyclohexanone and cyclopentanone with suitable solvent such as carbontetrachloride. The solvent selected must be suitable for reaction condition and temperature. All the three brominated carbazole derivatives A, B & C were further acetylated using bromoacetylbromide in DMF as a solvent.

The formation of various compounds were identified using thin layer chromatography followed by column chromatographic purification. All the synthesized compounds have been characterized by various spectral techniques *Viz*, UV-visible, FTIR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy. The synthesized compounds 2, 4 & 6 found to have excellent antibacterial activity. Among all the synthesized compounds 2, 4 & 6 compound 4 found to exhibit excellent antibacterial activity than other compounds.

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