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Antimicrobial and Antimycobacterial Activity of Some Quinoxalines 'N' Bridgehead Heterocycles

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Quinoxalin-2,3-diones (**1**) on treatment with *o*-phenylenediamine afforded 6,11-dihydro-5,6,-11,12-tetraazanaphthacene (**3**). 2,3-Dichloroquinoxaline (**2**) on condensation with anthranilic acid, *o*-phenylenediamine and sodium azide yielded *bis*[quinazolino(3,2a)quinoxaline]-11,18-diones (**4**), *bis*[benzimidazolo(1,2a)quinoxaline] (**5**) and *bis*-[1,2,3,4-tetrazolo (1,5a)quinoxaline] (**6**), respectively. The structures have been established by IR, mass spectral and elemental analysis. These compounds have been evaluated for their antibacterial, antifungal and antitubercular activity.

Key Words: Bridgehead quinoxaline, Antimicobaterial.

INTRODUCTION

Condensed heterocycles of quinoxalines have become attractive targets in synthetic and medicinal chemistry due to their significant biological activities[1,2]. Encouraged by previous reports regarding the similar broad spectrum antimicrobial properties of quinazoline[3] benzimidazole[4] and tetrazole[5], the present work has been undertaken on the synthesis of some bridgehead heterocyclics of quinoxalines. The medicinal importance of *bis*-disubstitution and bridgehead nitrogen atom stimulated the considerable interest in exploring the possible synthons of *bis*-condensed heterocyclics, in which a biological active quinoxaline is fused to two other biological active quinazoline/benzimidazole/tetrazole moieties[6]. With the above cited view we report herein some condensed heterocycles from quinoxalin-2,3-diones and 2,3-dichloro quinoxaline along with their antibacterial, antifungal and antitubercular activities.

EXPERIMENTAL

TLC was seen on silica gel G plates using toluene:ethyl acetate (9:1) as irrigant. Melting points are determined by open capillary method and are uncorrected. IR (KBr ν_{max}, cm^{-1}) spectra were recorded on FT-IR spectro-

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photometer at the resolution of 4 cm^{-1}. Mass spectra were scanned on a Joel Jmx.Dx-300 spectrometer operated at 70 eV.

Synthesis of compound 3: An equimolar quantities of quinoxalin-2, 3-dione (0.01 mol) and *o*-phenylenediamine (0.01 mol) was refluxed in DMF for 5 h. The resultant reaction mixture was cooled and poured on the crushed ice. The solid separated was dried and recrystallized from ethanol. Yield: 64 %, m.p. 280 ºC (Found: C, 71.43; H, 4.51; N, 24.14, $C_{12}H_{10}N_4$ requires C, 71.78; H, 4.30; N, 23.92). IR (KBr, ν_{max}, cm^{-1}): 3012, 3009 (C-H *str.*), 1615 (C=N *str.*), 759 (C-H out of plane deformation), ms: m/z 234 (M^+, 23 %).

Synthesis of compound 4: 2,3-Dichloroquinoxoline (0.01 mol) and anthranillic acid (0.01 mol) was placed in 250 mL round bottom flask containing 30 mL of glacial acetic acid. Then, the reaction mixture was refluxed for 6 h. The resulting cooled reaction mixture was poured in the ice water and solid precipitate was separated. The above crude product was recrystallized from ethanol to give compound **4**. Yield: 65 %, m.p. >300 ºC (Found: C, 72.58; H, 3.56; N, 15.14, $C_{22}H_{12}N_4O_2$ requires C, 71.52; H, 3.32; N, 15.38). IR (KBr, ν_{max}, cm^{-1}): 3010, 3015 (C-H *str.*), 1685 (C=O *str.*), 1614 (C=N *str.*), 761 (C-H out of plane deformation), MS: m/z 364 (M^+, 10 %).

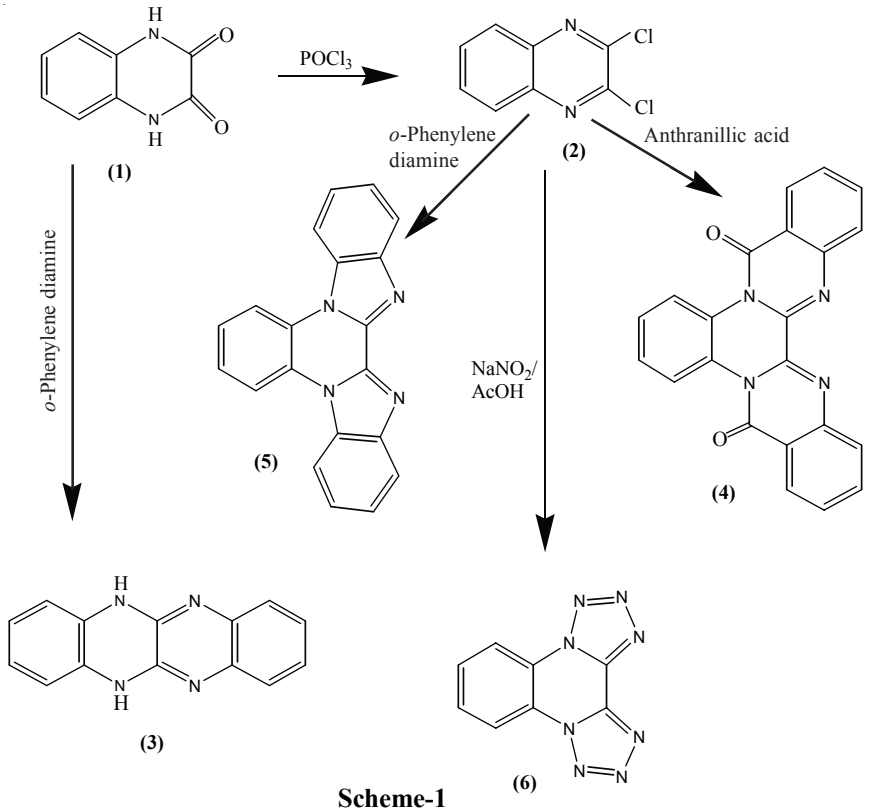
Synthesis of compound 5: 2,3-Dichloroquinoxaline (0.01 mol) and *o*-phenylenediamine (0.02 mol) in 25 mL of DMF was heated at 200 ºC in an oil bath until the evolution of ammonia was ceased. The mixture was cooled and poured on to crushed ice to give crude compound (**5**) and recrystallized from methanol. Yield: 62 %, m.p. 258 ºC (Found: C, 77.51; H, 4.12; N, 18.77, $C_{22}H_{16}N_4$ requires C, 77.91; H, 3.92; N, 18.17). IR (KBr, ν_{max}, cm^{-1}): 3010, 3004 (C-H *str.*), 1613 (C=N *str.*), 756 (C-H out of plane deformation), MS: m/z 308 (M^+, 5 %).

Synthesis of compound 6: 2,3-Dichloroquinoxaline (0.01 mol) in 20 mL of ethanol was treated with 0.03 mol of sodium nitrite and 10 mL of glacial acetic acid. The reaction mixture was heated under reflux until the brown colouration was appeared. The reaction mixture was cooled and keep overnight for crystallization. The formed crystals were separated and recrystallized from rectified spirit. Yield: 69 %, m.p. 235 ºC (Found: C, 65.54; H, 3.72; N, 22.58, $C_{12}H_{10}N_4$ requires C, 64.91; H, 3.27; N, 22.17). IR (KBr, ν_{max}, cm^{-1}): 3012, 3009 (C-H *str.*), 1614 (C=N *str.*), 759 (C-H out of plane deformation), MS: m/z 234 (M^+, 23 %).

RESULTS AND DISCUSSION

The required compounds quinoxalin-2,3-dione (**1**) and 2,3-dichloro quinoxaline (**2**) were prepared in crystal form following the reported method[7]. Condensation of **1** with *o*-phenylenediamine gave 6,11-dihydro-5,6,11,12-tetraazanaphthacene (**3**). The absence of absorption band at 1680

cm^{-1} for C=O stretching is in good agreement with assigned structure **3**. Condensation of **2** with anthranillic acid furnished compound **4**. The absence of absorption band at 998 cm^{-1} (C-Cl stretching) and the appearance of band at 1685 cm^{-1} (C=O stretching) suggesting the condensed cyclic system of **4**. Fusion of compound (**2**) with *o*-phenylenediamine afforded compound **5** and its structural assignment was supported by evolution of ammonia during reaction progress and absence of absorption band at 998 cm^{-1}. The compound **2** was condensed with sodium azide in the presence of acetic acid to give compound **6** and it was supported by the presence of sharp intense absorption band at 1614 cm^{-1} (C=N) and disappearance of 998 cm^{-1}. The assigned structures of the compound were well established by bathochromic shift λ_{max}, IR, mass spectral and elemental analysis. The compound purity was determined on TLC plate. Synthetic route for the above synthons was shown in **Scheme-I**.



Scheme-1

Antimicrobial activity: All the condensed synthons were evaluated for antimicrobial activity against the gram-positive bacteria *Staphyllococus aureus* and *Bacillus subtilis*, the gram-negative *Psudomonas aeroginosa*

and *Proteus vulgaris*, the fungi *Aspergillus niger* and the *Mycobacterium tuberculosis* $H_{37}R\nu$ species. Antibacterial and antifungal screening was carried out by agar plate disc diffusion method[8] at 100 μg/disc concentration and its results were reported as zone of inhibition in millimeter. The antitubercular screening was performed by Microplate alamar blue assay (MABA) method[9] at 6.25 μg/mL concentration. DMSO was used as solvent. Nalidixic acid (100 μg/disc) and clotrimazole (50 μg/disc) were used as standard, respectively for antibacterial and antifungal screening. The *in vitro* antimicrobial activity revealed that the tetraazanaphthacene (**3**) exhibited comparable broad spectrum antibacterial activity may be due to linear tetracyclic moiety. The tetrazole condensed quinoxaline **6** was found to shown moderate antibacterial and antifungal activity while benzimidazole **5** and quinazoline condensed systems **4** exhibited antifungal activity alone. Hence it was observed that antibacterial spectrum of quinoxalines found to be diminished when the cyclic tautomeric -NH- transformed into tertiary state by cyclization. The compound **6** showed antitubercular activity with 50 % inhibition and followed by the compound **4** with 24 % inhibition at 6.25 μg/mL concentration. However it was noted that the antitubercular and antifungal activity was found to be independent of the state of nitrogen in quinoxaline condensed systems.

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