Section E

Synthesis of 6-Chloro-7-(2,3-dichloro-phenoxy)-2,3-disubstituted-quinoxaline

Interest in the medicinal properties of quinoxalin-2-ones has stimulated our research in this field. Recently L. Sechi and co-authors reported the synthesis and biological activities of quinoxalin-2-ones and 12 pyrido[2,3-g]quinoxalin-2-ones. Among the quinoxalin-2-one series, we have observed that compounds bearing a carboxyethyl at C-3 and a CF$_3$ group or a morpholine ring in the benzo-moiety were moderately active against *Escherichia coli* and *Pseudomonas aeruginosa*, respectively, while those with an ethyl at C-3 and a CF$_3$ group in the benzo-moiety exhibited activity against *P. aeruginosa*. Introduction of a CH$_2$Br group at C-3 and a CF$_3$ or a NO$_2$ group in the benzoi moiety exhibited activity against *Staphylococcus aureus* and *Candida spp.*, respectively. The CF$_3$ group at both C-3 and the benzo-moiety of quinoxalinones showed to maintain this activity against *C. albicans* and *C. parapsilosis spp.*, while a CF$_3$ group at C-3 and Cl atoms in the benzo-moiety exhibited activity against *S. aureus*. Among the pyrido[2,3-g]quinoxalin-2-one series, we have observed that compounds bearing substituents such as a alkyl, CF$_3$ or CH$_2$Br group at C-3 or C-2 and Cl atom at C-5 exhibited both antibacterial and anticandida activities.

Present Work

These results prompted us to continue our investigation on quinoxaline in order to achieve additional data for a structure-activity relationship study. In this context, in order to evaluate if the concomitant presence of two favorable substituents in the benzo-moiety might improve biological activity, we have prepared a new series of quinoxalin-2-ones bearing a chlorine atom in the benzo-moiety and a ether linkage containing Cl substituted benzo moiety group in 6
position. Furthermore, we have synthesized the 6-Chloro-7-(2,3-dichloro-phenoxy)-2,3-disubstituted-quinoxaline in order to verify if this type of biological activity was maintained or not on the quinoxaline scaffold.

Here we wish to report simple and efficient method for the synthesis of 6-Chloro-7-(2,3-dichloro-phenoxy)-2,3-disubstituted-quinoxaline and to investigate their anti-microbial activity.

**General procedure**

To synthesize the title compounds following starting materials have been used

1. Amines
   a. 4-Chloro-5-(2,3-dichloro-phenoxy)-benzene-1,2-diamine

2. Dicarbonyl compound
   a. Benzil
   b. 4,4’-dimethylbenzil
   c. 4,4’-dimethoxybenzil
   d. 4,4’-dibromobenzil
   e. Oxalic acid
   f. Diethyl oxalate
   g. Oxalyl Chloride
   h. Glyoxal

3. Benzoin

**6-Chloro-7-(2,3-dichloro-phenoxy)-2,3-disubstituted-quinoxaline (3a-3i)**

Equimolar (10 mmol) amount 4-Chloro-5-(2,3-dichloro-phenoxy)-benzene-1,2-diamine and substituted dicarbonyl compound in ethanol was heated about 65°C for appropriate time (mention in table V.) The reaction was monitored by TLC.
After completion of reaction, the reaction mixture was poured into ice water and the precipitated solid was collected by filtration, washed with cold alcohol and the product was purified by column chromatography (PE/EtOAc, 9:1) to afford pure compound.

Structure of the newly synthesized compounds was established by the spectral analysis.
Scheme I $E_1$

\[
\text{Cl} \quad \text{Cl} \quad \text{O} \quad \text{NH}_2 \quad + \quad \text{O} \quad \text{O} \quad \text{R} \\
\text{Cl} \quad \text{Cl} \quad \text{Cl} \quad \text{NH}_2 \quad \text{NH}_2 \quad \text{R} \\
\text{(1)} \quad \text{Cl} \quad \text{Cl} \quad \text{O} \quad \text{N} \quad \text{R} \\
\text{EtOH} \quad 60^\circ C \\
\text{Cl} \quad \text{Cl} \quad \text{O} \quad \text{N} \quad \text{R} \\
\text{(3a - 3e)}
\]

Scheme I $E_2$

\[
\text{Cl} \quad \text{Cl} \quad \text{O} \quad \text{NH}_2 \quad + \quad \text{O} \quad \text{R} \\
\text{Cl} \quad \text{Cl} \quad \text{Cl} \quad \text{NH}_2 \quad \text{NH}_2 \quad \text{R} \\
\text{(1)} \quad \text{Cl} \quad \text{Cl} \quad \text{O} \quad \text{N} \quad \text{R} \\
60^\circ C \quad \text{EtOH} \\
\text{Cl} \quad \text{Cl} \quad \text{O} \quad \text{N} \quad \text{R} \\
\text{(3f - 3i)}
\]
Experimental protocol
6-Chloro-7-(2,3-dichloro-phenoxy)-2,3-diphenyl-quinoxaline (3a)
Equimolar (10 mmol) amount of 4-Chloro-5-(2,3-dichloro-phenoxy)-benzene-1,2-
diamine and benzoin in ethanol and heated about 65°C for 90 minutes. After
completion of reaction, the reaction mixture was poured into ice water and the
precipitated solid was collected by filtration, washed with cold alcohol and the
product was purified by column chromatography (PE/EtOAc, 9:1) to afford 3a.
Yield 75%, M.P. 245°C
All other compounds of this series were synthesized by following above
procedure. The physical data of these compounds have been recorded in Table I D.
Discussion of spectra
6-Chloro-7-(2,3-dichloro-phenoxy)-2,3-diphenyl-quinoxaline (3a)
IR spectra of some of the representative compounds of this series have been
scanned on JASCO spectrophotometer using KBr pellets. Chemical shifts are
reported in cm⁻¹.

1034  (-C-O-C-) stretching
1107  C-Cl stretching
1452  C=N stretching
1611  C=C aromatic stretching
3030  C-H aromatic stretching

¹H NMR spectra were recorded on Varian Gemini 200 MHz spectrometer.
Chemical shifts are reported in δ units (ppm) relative to TMS as internal standard
using DMSO-d₆ as a solvent.

  7.1-7.6   13 H, m (aromatic)
  8.25      2H, m, H-5,8

Electron spray ionization mass spectra (ES-MS) were recorded on Water-
Micromass Quattro II spectrometer.
Mass (ES/MS): m/z 477 (M+H)⁺