SUMMARY

CHAPTER 1: A SELECT REVIEW OF THE REACTIONS OF O-PHENYLENEDIAMINES WITH CARBONYL DERIVATIVES AND THEIR EQUIVALENTS.

This chapter presents a select summary of the reactions of o-phenylenediamines with carbonyl compounds and their equivalents: (a) monocarbonyls, (b) 1,2-dicarbonyls, (c) 1,3-dicarbonyls, (d) 1,4- and 1,5-dicarbonyls and (c) α,β-unsaturated carbonyls for the generation of heterocyclic structures. The structures thus designed include benzimidazoles (1) and its derivatives, quinoxalines (2), 1,5-benzodiazepines (3) and 1,10-phenanthrolines (4). Representative cases offering interesting mechanistic features are discussed.
CHAPTER 2: SYNTHETIC APPROACHES TO QUINOXALINES, BENZIMIDAZOLES AND PYRROLOBENZIMIDAZOLES.

This chapter deals with formation of quinoxalines (9, 31, Scheme 1, 4), benzimidazoles (18, 20-22, Scheme 2), pyrrolobenzimidazoles (17 & 25, 26, Scheme 2, 3) from the reaction of o-phenylenediamines with maleic anhydride derivatives.

1. The reaction of o-phenylenediamine and its nuclear as well as N-substituted derivatives with maleic anhydride (Scheme 1) results in formation of o-aminomaleanilic acids (7a-e) or dimaleanilic acid (13a) depending on reaction conditions. The monomaleanilic acids 7a-e obtained were cyclized to 2-oxo-quinoxalines (8a-e) via an intramolecular Michael-type addition. These acids were further converted (P₂O₅/ROH) to the corresponding esters (9a-e). The latter could also be prepared directly from o-aminomaleanilic acids (7a-e) and P₂O₅/ROH under similar reaction conditions combining cyclization and esterification in one-step.

2. Reactions of o-PDA with dimethylmaleic anhydride (15a) and methoxyphenylmaleic anhydride (15b) afforded directly the corresponding N-(o-aminophenyl)maleimides (16) in excellent yields. The amine function present in maleimides 16 exploited for further conversions. Intramolecular dehydrative cyclization of 16 afforded pyrrolobenzimidazoles (17). These were further treated with different nucleophiles (alkali, MeOH, amines) to generate benzimidazolyl acrylic acids 18 and their esters (20) and amides (21, 22). The condensation of amino function with carbonyl in unsymmetrical imides (16e-h) is regiospecific. The cyclization takes place at the carbonyl (a) in (16e-h) next to the methoxy group. This was
confirmed by treating the pyrrolobenzimidazole 16e-g with conc HI when it led to formation of 2-phenylacetylbenzimidazole 19e-g as the sole product (Scheme 2).

3. Acetylation of o-aminomaleimides 16 gave N-(o-acetamidophenyl) maleimides (23) and its formylation gave N-(o-formamidophenyl) maleimides (24a-c). These derivatives were further cyclized to angular acetoxy pyrrolobenzimidazoles 25 and 26a (Scheme 3). Such structures constitute interesting precursors to generation of azamitomycin congeners.

4. Treatment of o-phenylenediamine with maleimides (29) and isomaleimides (30) exclusively led to the corresponding N-phenyl-1,2,3,4-tetrahydro-2-oxo-quinoxaline acetanilides (31). However, the reaction of maleanilic acids (27a-f) and methylnmaleanilates (28) with o-PDA in refluxing ethanol afforded in each case mixtures of quinoxalines 31 and corresponding trans isomers 32 and 33 (Scheme 4). However, reactions of anilic acids with o-PDA in refluxing acetic acid led to formation of the corresponding acetanilide (34).

5. o-Aminomaleanilic acids (36-37) obtained from methyl and phenylnmaleic anhydride (35) were also sought to be studied to examine the regiochemical preference of the reaction. Unfortunately, the mixture of the acids (36-37) obtained could not be separated either as such or after their conversion to 2-oxoquinoxalines, either as carboxylic acids or their esters (Scheme 5).
Scheme 1

X R
a. H H
c. NO₂ C₂H₅
e. NO₂ Ph
b. NO₂ II
d. NO₂ CH₂Ph

i. Ether, MA, (2 hr), then RT, 15 min (for 5a); Ether, RT, 7-8 hr (for 5b-e)

ii. MA, Ether, RT, 1 hr (for 7a→13a and 12a→10a)

iii. Ether, RT, 1 hr, 5a:6=1:2 (5a→7a)

iv. H₂O, reflux, 2 hr (for 8a); AcOH, reflux, 2 hr (for 9b-e)

v. P₂O₅, anhydrous methanol, reflux, 3 hr (for 9a-c)

vi. H₂O, dil HCl (catalytic) Ac₂O, RT, 15 min (for 10a)

vii. Ac₂O, anhydrous NaOAc, Δ, waterbath, 15 min or Ac₂O, anhydrous NaOAc, RT 8 hr (for 11a)
Scheme 1

14 + 15 → 16

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<tr>
<th>X</th>
<th>Y</th>
<th>R</th>
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<tr>
<td>a</td>
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1. Ethanol, reflux, 30 min (for 16a-c and 16e-g) or DMF/ethanol, heat, 95°, 1 hr (for 16a & 16h)

2. AcOH, reflux, 20-30 min (for 17a-h)

3. aq. NaOH or KOH (2N), RT, 30 min (for 18a-d) or ethanol, KOH (2N), reflux, 2-3 hr (for 18e-h)

4. MeOH/conc H₂SO₄, reflux, 3-4 hr (for 20a-h)

5. CHCl₃/NMe₂, RT, 2 hr (for 21a-d) or CHCl₃/morpholine, RT 2 hr (for 22a-d)

6. AcOH:H₂O(1:1), reflux, 2 hr (for 18a-d)

7. Conc HI, reflux, 4 hr (for 19e-g)

8. Heat to m.p. or Ac₂O, heat (for 17a)
Scheme 3

$\text{X} \quad \text{Y} \quad \text{R} \quad \text{R}^1$

\begin{align*}
\text{a.} & \quad \text{H} \quad \text{H} \quad \text{Me} \quad \text{Me} \\
\text{b.} & \quad \text{Me} \quad \text{H} \quad \text{Me} \quad \text{Me} \\
\text{c.} & \quad \text{Cl} \quad \text{H} \quad \text{Me} \quad \text{Me} \\
\text{d.} & \quad \text{H} \quad \text{NO}_2 \quad \text{Me} \quad \text{Me}
\end{align*}

$\text{X} \quad \text{Y} \quad \text{R} \quad \text{R}^1$

\begin{align*}
\text{e.} & \quad \text{H} \quad \text{H} \quad \text{OMe} \quad \text{Ph} \\
\text{f.} & \quad \text{Me} \quad \text{H} \quad \text{OMe} \quad \text{Ph} \\
\text{g.} & \quad \text{Cl} \quad \text{H} \quad \text{OMe} \quad \text{Ph} \\
\text{h.} & \quad \text{H} \quad \text{NO}_2 \quad \text{OMe} \quad \text{Ph}
\end{align*}

1. $\text{Ac}_2\text{O}$, 2 hr, RT (for 23a-c and 23e-g);
   $\text{Ac}_2\text{O}$, reflux, 1 hr (for 23d and 23h).

11. $\text{HCO}_2\text{Et}$, $\text{AcOH}$, reflux, 12 hr (for 24a-b).

111. $\text{Ac}_2\text{O}$, $\text{NaOAc}$, reflux, 1-3 hr. (for 25a-h and 26a).
Scheme 4

1. o-PDA, EtOH, reflux, 2-5 hrs.

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CHAPTER 3 : EXPERIMENTAL DETAILS OF THE WORK

The work has involved preparation of large number of starting materials and generation of eighty five new compounds. Adequate evidences are presented to establish the structure of new compounds through spectral/analytical evidences and chemical conversions as and when appropriate.

Scheme 5

\[ R = \text{CH}_3 \quad \text{a.} \quad R = \text{Ph} \]

1. Ether, add MA (2 hr), then RT, 15 min