Reaction of 3-Benzylideneephthalide with Diamines and \( p \)-Aminophenylicarboxylic Acids & Antimicrobial Activities of the Products

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Summary: Bis-(2-methylene-3-benzal phosphthalimidine) II, desoxybenzoin-o-(4'-aminophenyl) carboxamide III and 2-(substitutedphenyl)-3-benzal phosphthalimidines of type IV and V were obtained via interaction of corresponding diamines with 3-benzylideneephthalide I. Condensation of \( C_6H_4(NH_2)_2 \) -1,2 with I gave fused benzimidazoisoindol derivative VII as anomalous product.

Benzal phosphthalimidines with \( p \)-carboxylate of type VIIIa-c are also prepared. Their IR, PMR and Mass spectra were also studied. III and VIIIb were found to exhibit activity against Gram-positive, Gram-negative, yeast and filamentous fungi.

Although many reactions of 3-benzylideneephthalide I [1] with several nucleophilic reagents have been investigated [2-8], but reactions of I with ethylenediamine, phenylendiamines and \( p \)-aminophenylcarboxylic

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acids have not been studied. In the present investigation, action of these reagents on I have been studied and their antimicrobial activities [9] were also discussed.

Condensation of I with ethylenediamine under mild conditions furnished only one product II. Elemental analysis of this product showed a value compatible with molecular formula C$_{32}$H$_{42}$O$_2$N$_2$ which indicates that one mole of ethylenediamine reacted with two moles of I. The IR spectrum of this product showed νC=O as a broad band at 1670 cm$^{-1}$ and νC-H aliphatic at (2920 - 2840 cm$^{-1}$) respectively. The mass spectrum showed a molecular ion peak at m/z 468 (M$^+$) together with a base peak at m/z 248 and other peaks at m/z 395, 394, 377, 288, 232 and 221. The above findings led to the formulation of this product as Bis-(2-methylene-3-benzalphtalimidine) II. However, condensation of I with p-phenylenediamine in glacial acetic acid containing fused sodium acetate furnished two products. Elemental analysis of these products showed values compatible with molecular formulae C$_{21}$H$_{18}$N$_2$O$_2$ and C$_{23}$H$_{18}$N$_2$O$_2$.

The IR spectrum of one of the products (C$_{21}$H$_{18}$N$_2$O$_2$) showed absorption bands at 3425 (νNH$_2$), 3337 (νNHCO) and at 1675 cm$^{-1}$ (νC=O). The mass spectrum showed a molecular ion peak at m/z 330 (M$^+$) together with a base peak at m/z 312.

The above findings led to the formulation of this product as desoxybenzoin-o-(4'-aminophenyl) carboxamide III.

The second product C$_{23}$H$_{18}$N$_2$O$_2$ was assigned the structure 2-(p-acetaminophenyl)-3-benzalphtalimidine IV on the basis of spectral data. Its IR spectrum showed absorption bands at 3330 (νNH) and at 1690 cm$^{-1}$ (νC=O). The PMR spectrum of this compound exhibited signals at δ 2.1 (3H, s, COCH$_3$), 6.48 [1H, s, (-C=CH-)] and 7.1 - 8.3 [14H, m, Ar - H & NH] ppm. The mass spectrum showed a molecular ion peak at m/z 354 (M$^+$) (100 %) as a base peak together with other peaks at 312, 311, 296, 295, 277, 235, 192, 150, 108, 106 and 91.

It is clear that 3-benzylidenephthalide I must have opened with p-phenylenediamine to give III which underwent cyclization with subsequent acetylation of the free amino group to phthalimidine compound IV.

Interaction of I with 0-nitro-p-phenylenediamine furnished the corresponding 2-(0-nitro-p-aminophenyl) 3-benzalphtalimidine V. The structure was supported by analysis, IR spectrum showed νCO at 1710 as strong absorption band, νNH at 3340, 3490 and νNO$_2$ at 1375 and 1520 cm$^{-1}$. The PMR spectrum of this compound showed five sets of signals at δ 6.28 [2H, s, NH$_2$ (exchanged with D$_2$O)], 6.33 [1H, d, Hd (which showed long range spin coupling with H*)] (JHdH$^*$ = 2.68Hz)] [10], 6.93 (1H, d, Hb; JHbc = 8.57Hz), 8.12 [2H, confused signal, (Ha & H*)] and at 7.20 - 7.82 (9H, m, Ar-H) ppm. The proton Hc appeared as a doublet at δ = 7.85 ppm, after shaking with D$_2$O. The mass spectrum shows molecular ion peak at m/z 357 (100%) as base peak together with other peaks at 339, 323, 309, 294, 214, 77, 75 and 73.

On the contrary the interaction of I with 0-phenylenediamine in glacial acetic acid in the presence of fused sodium acetate furnished one product only. Elemental analysis and both its
IR and PMR spectra confirmed that this product may be assigned structure 6-((benzal)benzimidazo[2,3-c]isindolo-10a-ol VII rather that the expected structure VI which could not be isolated. The IR spectrum of VII shows the disappearance of νC=O, while PMR spectrum showed two absorption signals at δ 4.55 and 7.2 - 8.2 in the intensity ratio 1:15. The first signal at δ4.55 [1H, broad signal (exchangeable with D2O), OH] and the second signal at δ7.2 - 8.2 [15H, m, (Ar - H, -C = CH -, NH)] ppm.

The formation of product VII was rationalized through the following sequence:

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Table 1: Characterization Data of Various Compounds prepared

<table>
<thead>
<tr>
<th>Comps</th>
<th>M.P. °C</th>
<th>Formula</th>
<th>Analysis</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CS</td>
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<tr>
<td>I</td>
<td>240-242</td>
<td>C22H24N2O2</td>
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<td></td>
<td></td>
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<td>82.05</td>
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<tr>
<td>III</td>
<td>220</td>
<td>C21H18N2O2</td>
<td>76.12</td>
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<td></td>
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<td></td>
<td>76.36</td>
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<tr>
<td>IV</td>
<td>260-262</td>
<td>C23H16N2O2</td>
<td>77.99</td>
</tr>
<tr>
<td></td>
<td>(dec.)</td>
<td></td>
<td>77.97</td>
</tr>
<tr>
<td>V</td>
<td>192-194</td>
<td>C21H15N3O3</td>
<td>70.46</td>
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<td></td>
<td></td>
<td>70.59</td>
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<tr>
<td>VII</td>
<td>158-160</td>
<td>C21H16N2O</td>
<td>80.49</td>
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<td></td>
<td></td>
<td>80.77</td>
</tr>
<tr>
<td>VIIIa</td>
<td>96-98</td>
<td>C24H19N3O</td>
<td>78.10</td>
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<td>78.05</td>
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<tr>
<td>VIIIb</td>
<td>204-206</td>
<td>C23H17N3O</td>
<td>77.55</td>
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<td>77.75</td>
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<td>VIIIc</td>
<td>230</td>
<td>C24H18N4O4</td>
<td>72.50</td>
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</table>

* compound VIIIa crystallised from petroleum ether (60-80°C).
* compounds VIIIb, c crystallised from ethanol.

In a similar fashion, condensation of I with ethyl p-aminobenzoate, p-aminophenylacetic acid and with p-aminohippuric acid was successful and the corresponding benzylidene-phthalimidines VIIIa-c with p-carboxylate group were obtained.

The assignment of structure VIII was based on analysis, IR measurements which showed νC=O at 1710, 1760 cm⁻¹, νC-H (aliphatic) at (2930...
Antimicrobial Activity:

Antimicrobial testing of the above mentioned compounds was carried out and it was found (Table-2) that compound VIIIb showed activity against a number of Gram-positive bacteria; Micrococcus luteus (maximum activity) (++++) with MIC = 7.5 µg/ml, Bacillus subtilis (moderate activity) (+++) with MIC = 10 µg/ml, Bacillus cereus (slight activity) (++) with MIC = 12.5 µg/ml and against Gram-negative bacteria, Escherichia coli (slight activity (+)) with MIC = 12.5 µg/ml. Also MIC 12.5 µg/ml against unicellular yeast, Candida utilis and filamentous fungi, Trichophyton sp., while other compounds were inactive. Thus, it is obvious that the presence of free functional group (-CH₂COOH) at the 4ᵗʰ-position of 2-phenylphthalimidine part (compound VIIIb) causes a pronounced effect on the antimicrobial activity.

Experimental

The melting points are uncorrected, the IR spectra (Nujol) were measured on Perkin Elmer spectrophotometer, PMR spectra (CDCl₃) were measured on Varian PM 390 90MHz NMR spectrophotometer and Mass spectra on Micromass 168 V.G. Micromass Ltd. Analytical data were determined in the microanalytical unit, Leicester University, U.K.

Bis(2-methylene-5-benzenephthalimidine) II (Table 1):

A solution of I (4.44g; 0.02 mol) in abs. ethanol (20ml) was treated with ethylenediamine (0.02 mol) dropwise with occasional shaking. The reaction mixture was left aside up to 30°C overnight, the solid obtained was filtered off and recrystallised from ethanol to give II as colourless crystals (yield 26%).
Table-2: Antimicrobial Activity

(+ + + + = maximum activity, MIC 7.50; + + = moderate activity, MIC 10;
+ + = slight activity, MIC 12.5 and - = inactive).

<table>
<thead>
<tr>
<th>Type of Organisms</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VII</th>
<th>VIIIa</th>
<th>VIIIb</th>
<th>VIIIc</th>
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<tbody>
<tr>
<td>Gram-positive</td>
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<tr>
<td>Micrococcus luteus</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++++</td>
<td></td>
<td></td>
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<tr>
<td>Bacillus subtilis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
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<tr>
<td>Bacillus cereus</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>+</td>
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<tr>
<td>Gram-negative</td>
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<td>Escherichia coli</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Yeast</td>
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<tr>
<td>Candida utilis</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td></td>
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<tr>
<td>Fungi</td>
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<tr>
<td>Trichophyton sp.</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
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</table>

* Minimal inhibitory concentration (MIC in µg/ml).

Condensation of I with phenylenediamines: General Procedure:

A mixture of I (0.05 mol) and phenylenediamine compound (0.05 mol) in glacial acetic acid (30ml) containing (0.2g) freshly fused sodium acetate were heated under reflux for 6 hour, cooled and decomposed with dil. HCl.

a. In the case of p-phenylenediamine, the product obtained was treated with ethanol in which the yellow solid dissolved yielding III (28%). The insoluble residue on crystallisation from xylene gave IV (26%) as light brown crystals (Table 1).

b. In the case of o-nitro-p-phenylenediamine, the product was filtered and recrystallised from ethanol to give V as golden yellow needles (yield 52%) (Table 1).

c. In the case of o-phenylenediamine, the product was filtered and recrystallised from dil. ethanol to give VII as yellow needles (yield 40%) (Table 1).

Benzylideneephthalimidine-p-carboxylate (VIIIa-c) (Table 1):

The method was proceeded as above in the case of III, IV, V and VII.

Biological Screening (Table 2):

The compounds were tested against different types of Gram-positive bacteria (Micrococcus luteus, Bacillus subtilis, Bacillus cereus), Gram-negative bacteria (Escherichia coli), unicellular yeast (Candida utilis) and filamentous fungi (Trichophyton sp.) using the hole plate and filter paper disc method [11-13].

A quantitative assays were done on active compounds only.

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