**Synthesis of Some New Azomethines from 2-(4'-aminophenyl)-1-Methylbenzimidazole**

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This paper describes a series of azomethines obtained from 2-(4'-aminophenyl-1-methyl)-benzimidazole and various aromatic aldehydes. The condensing reaction optimum occurred by refluxing the reaction mixture, in ethanol, using acetic acid as catalyst. The obtained products were purified by recrystallization from organic solvents and by column chromatography on aluminium oxide. Azomethines structure was confirmed by FT-IR and NMR spectra.

Keywords: 2-p-aminophenyl-1-methylbenzimidazole, condensing reaction, Schiff Bases

The un-substituted 2-phenylbenzimidazoles functionalized in the phenyl ring are associated with significant pharmacological activity. The corresponding amines, the 2-(p-aminophenyl)-benzimidazoles among them, were tested for their inhibition action on the neoplasm [1]. Some of their derivatives have distinguished themselves as efficient drugs against some malignant and non-malignant proliferative diseases showing also immuno-suppressing effect in transplants [2, 3]. The condensation products of the amines showed anti-tuberculosis, anti-inflammatory, anthelmintic actions as well as regulating action on the central nervous system functions [4-6].

A previous article detailed our rather laborious trials which resulted in settling some convenient obtaining procedures of the 2-(p-aminophenyl)-benzimidazole and its m-amino substituted isomer [7]. A careful literature study took into consideration the already known methods [8-16]. Starting from literature, the reaction scheme for the reduction of the nitro derivatives has been chosen.

The conversion of the nitro compound to the amine was carried out with Na₂S in the presence of NaHCO₃ [7], in water-alcoholic solution. This method proves itself to be more convenient than the reductions with ammonium sulphide, stannous chloride and then the catalytically purified.

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**Experimental part**

**Materials and methods**

IR spectra were recorded on a Fourier Transform Digilab Scimitar Series spectrometer, in KBr pellets in the range 4000-400 cm⁻¹. The NMR spectra were registered on a Brüker WM 400 MHz spectrometer, in DMSO-d₆ solution. Melting points were measured using an electrical apparatus: a Boetius hot stage microscope BM2 and are uncorrected. Nitrogen elemental analyses were performed with a Carlo Elba Model M-1106.

All chemicals are of analytical grade, were obtained from commercial sources (Fluka, Merck etc.) and used without further purification.

Three reactants were obtained in the laboratory, the synthetic methods being carried out as following:

2-(4'-Aminophenyl)-1-methylbenzimidazole. The amine has been prepared from 2-(4'-nitrophenyl)-1-methyl-

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Azomethine with p-anisaldehyde. By cooling a yellow solid separated. From the evaporated filtrate, by resuming it in ethyl acetate, a supplementary amount of product has been separated. Purification was carried out by recrystallization (table 1) or by column chromatography, using a 9:1 (v/v) dichloromethane-isopropanol mixture as eluent.

Azomethine with p-tolylaldehyde. A yellow solid separated from the solution kept at room temperature for several days.

Azomethine with p-chlorobenzaldehyde. By cooling, in time, a light yellow product separated, that was washed on filter with small amount of ethanol. By chromatography with dichloromethane-isopropanol mixture 2 fractions were collected, dried up and then dispersed with ethyl acetate.

Azomethine with cinammaldehyde. The next day a yellow-orange substance separated which was solved in DMF or methyl acetate and precipitated with ethyl ether. Finally, the solid was recrystallized from o-xylene.

Azomethine with p-dimethylaminocinammaldehyde. After solvent vaporization a yellow product was obtained.

Azomethine with p-nitrocinammaldehyde. Product obtained by solvent vaporization was solved in chloroform and chromatographed with dichloromethane-isopropanol mixture as eluent. From the solution, by concentration, yellow crystals separated.

Results and discussions
The experimental protocol was aimed to study the reactivity of one of the 2-phenyl-benzimidazole amines, having the following structure (1):

Structure (1)

This amine is more basic than the derivative non-methylated at N1. Spectral data and theoretical calculus [21, 22] made evident that the bulky methyl group increase the non-planarity of the fundamental status of 2-phenyl-1-methyl-1H-benzimidazole, resulting in a conjugation loss of the π system. The 2-phenyl-1H-benzimidazole was also proved to have a planar conformation in its S0 status.

The estimation of the electronic and steric effects afforded the conclusion that the steric hindrances at the C2-C1' bond in the methylated amine causes the phenyl ring to be turned off from coplanarity, cancelling the conjugation and having a favourable effect on the basicity. The amine with the free NH group is less basic due to the planarity.

The behaviour of these two amines in various reactions might be interesting to follow, especially because they were previously very little investigated.

Attention was paid to the amine conversion into azomethines with extended conjugated structure, by condensation with aromatic aldehydes.

The reactions were carried out according to the scheme 1.

Scheme 1. Azmethines prepared from 2-(p-aminophenyl)-1methylbenzimidazoles

Table 1
AZOMETHINES DERIVATED FROM 2-(4'-AMINOPHENYL)-1-METHYLBENZIMIDAZOLE

<table>
<thead>
<tr>
<th>Comp</th>
<th>M.p., °C</th>
<th>η %</th>
<th>Purification solvent</th>
<th>Molecular Formula</th>
<th>Elemental Analysis %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>calc. N % exp.</td>
</tr>
<tr>
<td>2 a</td>
<td>270-285</td>
<td>94</td>
<td>ethanol, benzene, toluene</td>
<td>C23H22N4</td>
<td>15.82 15.95</td>
</tr>
<tr>
<td>2 b</td>
<td>213-215</td>
<td>85</td>
<td>ethanol, CHCl3, toluene</td>
<td>C21H14N4O2</td>
<td>15.73 15.85</td>
</tr>
<tr>
<td></td>
<td>218-220 (conam)</td>
<td></td>
<td>ethanol, o-xylene</td>
<td>C23H32N4O</td>
<td>17.46 17.58</td>
</tr>
<tr>
<td>2 d</td>
<td>178-180</td>
<td>76</td>
<td>ethyl acetate</td>
<td>C22H30N3</td>
<td>12.92 12.95</td>
</tr>
<tr>
<td>2 e</td>
<td>302-305</td>
<td>90</td>
<td>unsolv. ethanol, DMF+H2O</td>
<td>C21H17N2O</td>
<td>12.84 12.97</td>
</tr>
<tr>
<td>2 f</td>
<td>190-192</td>
<td>78</td>
<td>ethanol, toluene</td>
<td>C22H23N2O</td>
<td>12.32 12.44</td>
</tr>
<tr>
<td>2 g</td>
<td>195-198</td>
<td>70</td>
<td>ethanol</td>
<td>C22H18N6Cl</td>
<td>12.16 12.29</td>
</tr>
<tr>
<td></td>
<td>199-200 (conam)</td>
<td>70</td>
<td>ethanol, o-xylene</td>
<td>C22H23N6</td>
<td>12.46 12.58</td>
</tr>
<tr>
<td>2 h</td>
<td>205-207</td>
<td>70</td>
<td>ethanol</td>
<td>C22H23N6</td>
<td>14.73 14.81</td>
</tr>
<tr>
<td>2 i</td>
<td>168-170</td>
<td></td>
<td>ethanol</td>
<td>C22H23N6</td>
<td>14.73 14.81</td>
</tr>
<tr>
<td>2 j</td>
<td>196-198</td>
<td>82</td>
<td>cromat. CH2Cl2-isopropanol</td>
<td>C23H23N4O2</td>
<td>14.65 14.75</td>
</tr>
</tbody>
</table>
Such reactions are reversible and proceed under conditions of acid catalysis. The reactions were carried out with equimolar reagent ratio, by refluxing in ethanol and in the presence of acetic acid as catalyst. The azomethines thus obtained are given in table 1.

The reaction time was of 30 min. or 1 hour with the less reactive aldehydes (p-OH, p-CH₃O, p-CH₃, p-Cl). The obtained yields were between 71-90%, much depending on the product solubility in ethanol. The purification was made from organic solvents, such as: ethanol, toluene, o-xylene. A two solvents mixture was sometime used (DMF-ethylcether, ethyl acetate-ethylcether, toluene-petroleum ether). In most cases, a great amount of unsolved crystals remained after boiling in ethanol, showing a deeper colour and higher melting point. A component with lower melting point separated from the soluble fraction by cooling. Since the substances are soluble in few solvents, the recrystallizations were rather difficult. At the same time, the purification by column chromatography with aluminium oxide was applied.

The azomethines resulted as light-yellow (p-Cl, p-OH, p-CH₃) to deep yellow or even orange (p-NO₂) coloured compounds depending on the conjugated system extension and on the nature of the p-substituent (Y). Thus, with an electron-releasing group, e.g. dimethyl amino group, the electron shifting proceeds along the entire conjugated fragment up to the heterocyclic nitrogen atom, thus resulting the appearance of the internal amphionic structure 2a.

By having an electron-withdrawing substituent, such as the nitro group, the conjugated system is submitted to a competition between the strongly electron-withdrawing –NO₂ group and the C=N bond exhibiting a lower –M effect. It must also be specified the cis-trans isomeric effect at the substituted imino bond resulting in the existence of the stereoisomers presented below.

The implication of the cinnamic aldehyde and its p-substituted derivatives (Me₃N, NO₂-) led to polyenic molecules containing imino group as well as an ethylene bond.

The p-dimethylaminocinnamic aldehyde was synthetized by the condensation of p-dimethyl-amino-benzaldehyde with para aldehyde, in the presence of H₂SO₄. We also applied this method to obtain the p-nitrocinnamic aldehyde.

The structure of the azomethines 2 was investigated by the means of FT-IR and 1H-NMR spectral measurements. One of the characteristic bands in the IR spectra is generated by the νC=N valence vibrations. The azomethines are known to show absorption picks within the 1630-1690 cm⁻¹ range. In the conjugated molecules the band frequency decreases and the intensity increases. The spectra understudy show an absorption band of a medium or high intensity between 1622 and 1639 cm⁻¹ attributable to the νC=N vibrations. The benzene rings give the band between 1585 and 1597 cm⁻¹ corresponding to the νC-C vibrations and one or two absorptions between 3016 and 3082 cm⁻¹ generated by the ν=CH aromatic and azomethine vibrations.

<table>
<thead>
<tr>
<th>Comp</th>
<th>Characteristic bands, DMSO, δ (ppm), J(Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>3.08 (s, 6H, N(CH₃)₃); 3.91 (s, 3H, N-Ch₃); 6.77-6.74 (d, 2H, H-3', H-5'); J₆₇=8.937); 7.25 (m, 8H, H-5, H-6, H-3', H-5', H-2', H-6', H-4, H-7); 7.78-7.81 (d, 2H, H-2', H-6', J₆₇=8.937); 8.37 (s, 1H, N=CH)</td>
</tr>
<tr>
<td>2b</td>
<td>3.95 (s, 3H, N-Ch₃); 7.25 (m, 6H, H-5, H-6, H-3', H-5', H-2', H-6'); 7.40-7.43 (d, 2H, H-4, H-7, J₆₇=8.475); 8.11-8.13 (d, 2H, H-2', H-6', J₆₇=8.734); 8.26-8.28 (d, 2H, H-3', H-5', J₆₇=8.899); 8.62 (s, 1H, N=CH)</td>
</tr>
<tr>
<td>2c</td>
<td>3.95 (s, 3H, N-Ch₃); 7.27-7.38 (m, 2H, H-5, H-6); 7.44-7.54 (m, 3H, H-3', H-5', H-6'); 7.77-7.97 (m, 1H, N=CH); 8.78-9.94 (m, 2H, H-2', H-6'); 8.56-8.64 (m, 2H, H-4, H-7); 8.94-9.86 (s, 1H, H-5'); 9.1 (s, 1H, H-3')</td>
</tr>
<tr>
<td>2d</td>
<td>2.39 (s, 3H, CH₃); 3.87 (s, 3H, N-Ch₃); 7.14-7.15 (d, 2H, H-2', H-6', H-3', H-5', J₆₇=8.26, J₆₇=8.73); 7.74-7.83 (m, 6H, H-2', H-2', H-6', H-6', H-4, H-7, J₆₇=8.55, J₆₇=8.75, J₆₇=8.26); 8.45 (s, 1H, N=CH)</td>
</tr>
<tr>
<td>2e</td>
<td>3.87 (s, 3H, N-Ch₃); 6.90-6.86 (d, 2H, H-3', H-5', J₆₇=8.45); 7.23-7.25 (m, 2H, H-5, H-6, J₆₇=8.64); 7.33-7.37 (d, 2H, H-3', H-5', J₆₇=8.30); 7.55-7.67 (m, 2H, H-2', H-6', J₆₇=8.46); 7.77-8.11 (d, 2H, H-4, H-7, J₆₇=8.63); 7.83-7.87 (d, 2H, H-2', H-6', J₆₇=8.39); 8.52 (s, 1H, N=CH)</td>
</tr>
<tr>
<td>2f</td>
<td>3.81 (s, 3H, N-Ch₃); 3.87 (s, 3H, O-Ch₃); 7.04-7.08 (d, 2H, H-3', H-5', J₆₇=8.74); 7.24 (m, 2H, H-5, H-6); 7.35-7.39 (d, 2H, H-2', H-6', J₆₇=8.46); 7.65 (m, 2H, H-4, H-7); 7.84-7.88 (d, 2H, H-3', H-5', J₆₇=8.78); 8.78-8.92 (d, 2H, H-2', H-6', J₆₇=8.48); 8.56 (s, 1H, N=CH)</td>
</tr>
<tr>
<td>2g</td>
<td>3.88 (s, 3H, N-Ch₃); 7.24-7.27 (m, 2H, H-5, H-6, J₆₇=8.18); 7.41-7.45 (d, 2H, H-3', H-5', J₆₇=8.20); 7.57-7.61 (d, 2H, H-3', H-5', J₆₇=8.35); 7.63-7.67 (d, 2H, H-2', H-6', J₆₇=8.44); 7.87-8.11 (d, 2H, H-2', H-6', J₆₇=8.28); 8.09-8.19 (d, 2H, H-4, H-7, J₆₇=8.29); 8.71 (s, 1H, N=CH)</td>
</tr>
<tr>
<td>2h</td>
<td>3.98 (s, 3H, N-Ch₃); 5.00 (s, 1H, -CH₃); 5.70 (s, 1H, =CH-CH₃); 7.21-7.24 (m, 3H, H-4', H-3', H-5'); 7.48-7.56 (d, 2H, H-5, H-6); 7.61-7.71 (dd, 2H, H-2', H-6', J₆₇=8.62); 7.86-8.02 (d, 2H, H-3', H-5'); 8.42-8.48 (d, 2H, H-2', H-6'); 8.65-8.70 (dd, 1H, N=CH₃); 8.80-8.86 (m, 1H, H-7); 9.02 (s, 1H, H-4)</td>
</tr>
</tbody>
</table>
The methyl groups give two or more absorptions between 2846 and 2889 cm\(^{-1}\), and 2914 and 2985 cm\(^{-1}\), respectively, due to the aliphatic ν\(\text{CH}\) valence vibrations. The intense and very intense bands between 1365-1382 cm\(^{-1}\) and at about 1460 cm\(^{-1}\) attributable to the δ\(\text{CH}_3\) deformation vibrations are also noticeable. The spectra show also distinct absorptions given by the p-substituents (NO\(_2\), OCH\(_3\), Cl, etc.) and other bands generated by the ortho and para aromatic disubstitution which are rather difficult to identify.

The 1\(^{1}\)H-NMR spectra correspond entirely to the proton number and types in the azomethine structures.

The signals given by every compound are presented in table 2.

The presence of methyl protons (NMe\(_2\), OMe, N-Me) can be observed at rather low d values. The numerous aromatic protons were arranged according to the effects of the substituents in the ending phenyl ring.

Conclusions

Due to the pharmacological activity found for previously known 2-phenylbenzimidazoles we considered opportune to synthesize and characterize new compounds from the same class also exhibiting an azomethine group.

A series of reactants have been synthesized (p-aminophenyl benzimidazole, dimethylaminocinnamaldehyde and nitrocinnamaldehyde) using synthetic methods previously studied or from literature.

The p-aminobenzaldehyde has been condensed with various aldehydes, the reaction principle being the same, but the reaction details varying from one case to another.

The azomethines have been separated from reaction mixture and purified by recrystallization from ethanol or by column chromatography.

For the obtained Schiff bases the electronic migration effect and the cis-trans isomeric effect have been explained.

The final products have been characterized by the means of melting point and spectral analysis: FT-IR and 1\(^{1}\)H-NMR.

References


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