Synthesis of 2,2'-(*p*-Phenylene)bisbenzazoles Compounds From Terephthalohydroxamoyl Chloride

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In this study, synthesis of symmetric compounds of 2,2'-(*p*-phenylene)bisbenzothiazole, 2,2'-(*p*-phenylene)bisbenzimidazole and 5,5'-dimethyl-2,2'-(*p*-phenylene)bisbenzoxazole were benefited from the reaction of terephthalohydroxamoyl chloride with 2-amino-4-methyl phenol, *o*-aminothio phenol and *o*-phenylenediamin compounds. The structures of these compounds were confirmed by elemental analysis, mass, ^{1}H-NMR and FT-IR techniques.

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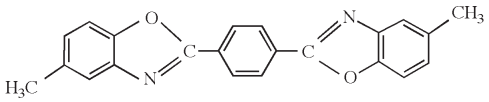
Introduction.

Generally, oxazoles have five-rings one of which contains one oxygen and one nitrogen atom. However, thiazoles and imidazoles are derivatives of oxazoles. Especially, oxazoles, imidazoles and thiazoles have been of growing interest in the medicine industry. Some derivatives of imidazole, for example histidine, β-4-imidazolylalanine or α-amino-β-4-imidazolylpropion are important structures with respect to aminoacids in human body. In addition, aneurine and thymine derived from thiazole are known as vitamin B. However, benzoxazoles and related combined hetereocycles such as benzimidazoles and benzothiazoles were studied for their antitumor, antiviral and antimicrobial activites. For example 2-(*p*-substituted-phenyl)-5-substitued-carbonylamino benzoxazole derivatives were synthesized and their antimicrobial activities were determined in comparison with several control drugs. The microbiological results showed that the compounds possessed a diffuse spectrum of antibacterial activity against these microorganisms. In addition, when quaternized to benzothiazolium salts, these compounds are especially active as antimicrobial, antihelmintic and antineoplastic agents and 2-alkylthio-6-aminobenzthiazoles have shown good antimycobacterial, antiyeast, anticandidous and antialgal activities. Tricyclazole is one of the benzothiazole derivatives associated with diverse biological activities such as application of potent anti-bacterial and fungicides for the control of Piricularia oryzae in the prevention of rice blast [1-3].

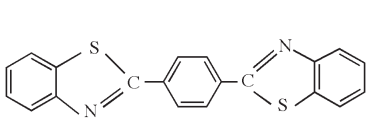
A large number of poly(benzoxazole)s and poly(benzothiazole)s are the most thermally stable polymers which contain highly rigid heterocycles in the backbone. Most of the symmetric bis-benzoxazole, bis-benzothiazole and bis-benzimidazole compounds are synthesized from carboxylic acid, acid anhydride and nitrile compounds by acting with 2-amino-4-methyl phenol, *o*-aminothiophenol, *o*-phenylenediamin compounds in the presence of PPA (polyphosphoric acid) [4].

The synthesis of one sided benzoxazole, benzthiazole and benzimidazole as a result of the reaction of hydroximoyl chloride with these amine compounds are present in literature, but there is no literature about the synthesis of symmetric bisbenzoxazole, bisbezthiazole and bisbenzimidazole from bishydroxamoyl chloride [5].

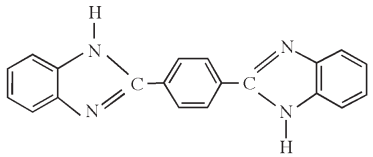
In the present study, the synthesis of symmetric bisbenzoxazole, bisbenzothiazole and bisbenzimidazole compounds have been reported. The molecular structures of these compounds are shown in Figure 1 were identified by FT-IR, mass, ^{1}H-NMR and elemental analysis.



5,5'-dimethyl-2,2'^{1}-(p-phenylene)bis(benzoxazole)
III: ($C_{22}H_{16}N_2O_2$)



2,2^1-(p-phenylene)bis(benzthiazole)
IV: ($C_{20}H_{12}N_2S_2$)



2,2^1-(p-phenylene)bis(benzimidazole)
V: ($C_{20}H_{14}N_4$)

Figure 1. Structures of synthesized symmetric bis-benzoxazole and its derevatives

Methods of Investigation.

Materials and Measurements.

All chemicals (Merck and Fluka) were in analytical grade and used without further purification. The ^{1}H-NMR spectra, mass spectra and elemental analysis for carbon, hydrogen and nitrogen were carried out in the Laboratories of the Scientific and Technical Research Council of Turkey (TUBITAK). Infrared spectra were recorded on a Perkin Elmer Model 1605 FT-IR spectrophotometer as KBr pellets in the region of 500-4000 cm^{-1}.

Synthesis of Terephthalaldoxime and Terephthalohydroximoyl Chloride.

In this study, terephthalaldoxime [$C_8H_8N_2O_2$] and terephthalohydroximoyl chloride [$C_8H_6Cl_2N_2O_2$] have been synthesized according to the methods in literature. The starting material of terephthalaldoxime was synthesized from terephthalaldehyde by the standard procedure. After that terephthalohydroximoyl chloride was obtained by passing chlorine gas (which was dried and passed under safe conditions) through dioxane or CCl_4 solutions of terephthalaldoxime [6,7]. The structures of terephthalaldoxime (I) and terephthalohydroximoyl chloride (II) are shown in Figure 2. IR (ν, cm $^{-1}$) (I) : 3167 ν (O-H), 3072 ν (C-H $_{arom.}$), 2988 (C-H $_{aliph.}$), 1480 ν (C=C), 982 ν (N-O). IR(ν, cm $^{-1}$) (II): 3234 ν (O-H), 3037 ν (C-H $_{arom.}$), 1458 ν (C=C), 998 ν (N-O).

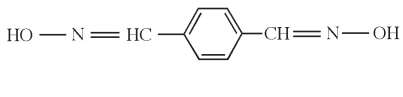
Values of III compound: LC/MS [m/z (rel. %)]: 341 (10), 340 (45), 325 (12), 309 (25), 300 (11), 293 (9), 281 (5), 266 (26), 252 (44), 251 (11), 227 (5), 180 (9), 145 (16), 113 (98), 79 (20). IR (ν, cm $^{-1}$): 3022 ν (C-H $_{arom.}$), 2921 ν (C-H $_{Aliph.}$), 1635-1615 ν (C=N$_{oxsazole\ ring}$), 1478 ν (C=C). ^{1}H-NMR (δ, ppm) (DMSO-d^6): 8.30 (s, 4H, C-H $_{Arom}$), 7.16-7.53 (m, 6 H, C-H $_{Arom.}$), 2.48 (s, 6H, C-H $_{aliph.}$).

Values of IV compound: LC/MS [m/z (rel. %)]: 346 (5), 345 (42), 344(10), 315 (20), 314 (89), 311 (29), 298 (5), 287 (18), 286 (96), 284 (25), 270 (6), 258 (10), 256 (25), 228 (8), 216 (5), 178 (5), 101 (57), 79 (8). IR (ν, cm $^{-1}$): 3054 ν (C-H $_{arom.}$), 1638-1618 ν (C=N$_{thiazole\ ring}$), 1481ν (C=C). ^{1}H-NMR (δ, ppm) (DMSO-d^6): 8.38 (s, 4H, C-H $_{Arom}$), 7.65 (q, 4H, C-H $_{Arom}$, J=3.13 Hz), 7.28 (q, 4H, C-H $_{Arom}$, J=3.20 Hz).

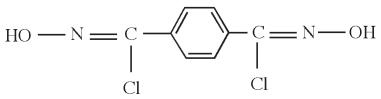
Values of V compound: LC/MS [m/z (rel. %)]: 311 (7), 310 (25), 309 100), 281 (7), 255 (9), 236 (5), 218 (14). IR (ν, cm $^{-1}$): 3413 ν (N-H), 3070 ν (C-H $_{arom.}$), 1637-1618 ν (C=N$_{oxsazole\ ring}$), 1437 ν (C=C). ^{1}H-NMR (δ, ppm) (DMSO-d^6): 8.32 (s, 4H, C-H $_{Arom}$), 8.21 (d, 2H, C-H $_{Arom}$, J=7.82 Hz), 8.13 (d, 2H, C-H $_{Arom}$, J=8.28 Hz), 7.60 (t, 2H, C-H $_{Arom}$, J=8.16 Hz), 7.52 (t, 2H, C-H $_{Arom}$, J=7.81 Hz), 7.37 (s, 2H, N-H $_{Arom}$).

Results and Discussion.

In general, the amidoximes and their derivatives were synthesized from the condensation reaction of some primary and secondary amines of hydroxamoyl chlorides



I: ($C_8H_8N_2O_2$)



I: ($C_8H_6Cl_2N_2O_2$)

Figure 2. Structures of terephthalaldoxime and terephthalohydroximoyl chloride

Synthesis of bis-Benzoxazole and its Derivatives.

Terephthalohydroximoyl chloride (0.30 g, 1.29 mmol) was dissolved in 15 ml ethanol. Aqueous solution of $NaHCO_3$ and 2.84 mmol of amine (0.30 ml *o*-aminothiophenol, 0.31 g phenylenediamine or 0.35 g 2-amino-4-methylphenol) were added to the solution. The mixture was stirred for about one week at room temperature and then a mixture of *o*-aminothiophenole was heated under reflux for three hours. Bisbenzoxazole deposited as solid was collected by filtration and recrystallized from dimethylformamide. Similar literature was used to synthesis the derivatives of bisbenzoxazole [5]. Some physical properties of synthesized compounds were tabulated in Table 1. Mass, FT-IR, and ^{1}H-NMR values of [5,5'-dimethyl-2,2'^{1}-(*p*-phenylene)bis-(benzoxazole)](III); [2,2^1(*p*-phenylene)bis-(benzthiazole)] (IV) and [2,2^1(*p*-phenylene)bis-(benzimidazole)] (V) are given as following.

[8]. Terephthalohydroximoyl chloride gave the heteroaromatic closing reaction with 2-amino-4-methyl phenol, *o*-aminothiophenol, phenyelenediamine, although *N*,*N*'-disubstituted amidoximes and their derivatives were synthesized by the condensation reaction of the same monomer with same primary amines at the same conditions. The synthesis of several bis(benzthiazoles, benzoxazoles and benzimidazoles) and related compounds were prepared by the reactions of 2-amino-4-methylphenol, *o*-aminothiophenol and phenyelene diamine with the dicarboxylic acid, anhydride or nitrile using polyphosphoric acid (PPA) and the reaction was completed in two hours with stirring as in literatures [4,9-18]. Benzoxazole and benzimidazole were prepared by the condensation reaction of *o*-aminothiophenol, phenyelenediamine of *O*-alkylated oxime and by the transformations of *O*-aminophenol in one of the literature [19].

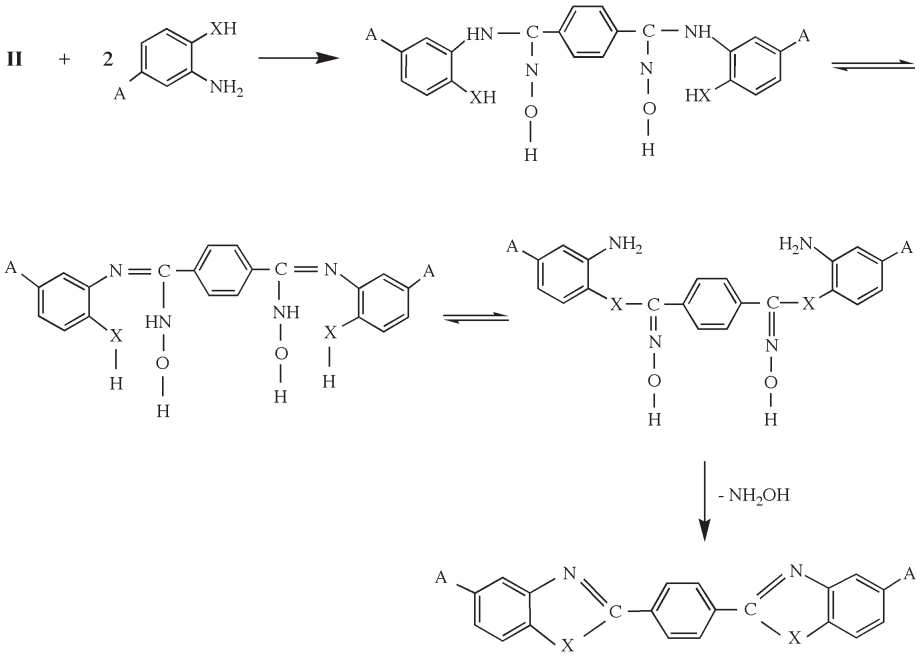
Table 1

Some physical properties and elemental analysis of the terephthalaldoxime, terephthalohydroxamoyl chloride, bis-benzoxazole derivatives.

Compound	Colour	M.p. (°C)	Yield %	Found (Calcd.) % C	H	N	Cl
$C_8H_8N_2O_2$	light yellow	223	83	58.17 (58.5)	4.61 (4.87)	17.0 (17.1)	- -
$C_8H_6Cl_2N_2O_2$	white	195	81	47.50 (47.76)	2.90 (2.99)	13.74 (13.9)	30.5 (30.6)
$C_{22}H_{16}N_2O_2$	yellow	310	90	77.5 (77.4)	4.60 (4.62)	8.24 (8.20)	- -
$C_{20}H_{12}N_2S_2$	light yellow	258	93	68.9 (68.7)	3.49 (3.50)	8.18 (8.24)	- -
$C_{20}H_{14}N_4$	Dark yellow	> 300	88	77.0 (76.7)	4.50 (4.45)	17.8 (17.5)	- -

In this study, as different from literature, symmetric bis-benzoxazole and its derivatives were obtained from these bishydroximoyl chlorides by acting with related amines [8]. The structures of bisbenzoxazoles and derivatives are shown in Figure 1 and their colors, melting points, results of elemental analysis are given in Table 1. Mechanism of the synthesized symmetric bis-benzoxazole and its derivatives are shown in Figure 3.

In the FT-IR spectra of 5,5'-dimethyl-2,2'-(*p*-phenylene)-bis(benzoxazole), bands at 3000-3022, 2863-2921, 1635-1615, 1571-1478 cm^{-1} were assigned to $\nu(CH_{arom})$, $\nu(CH_{aliph})$, $\nu(C{=}N_{oxsazole\ ring})$, and $\nu(C{=}C)$ the absorption bands respectively while that of 2,2'-(*p*-phenylene)-bis(benzothiazole) bands at 3054, 1638-1618, 1481 cm^{-1} were assigned to $\nu(CH_{arom})$, $\nu(C{=}N_{thiazole\ ring})$ and $\nu(C{=}C)$ absorption bands, respectively. In addition to this, in the FT-IR spectra of 2,2'-(*p*-phenylene)-bis(benzimidazole), bands at 3070-3200, 3413, 1637-1618, 1400-1437 cm^{-1} were assigned to $\nu(CH_{arom})$,$\nu(NH)$, $\nu(C{=}N_{imidazole\ ring})$, $\nu(C{=}C)$ the absorption bands, respectively [1-4,12]. Although $\nu(N\text{-}O)$ stretching vibrations appeared at about 980 cm^{-1} in the terephthalohydroximoyl chloride, these



III: X: O, A: CH_3 ($C_{22}H_{16}N_2O_2$)
IV: X: S, A: H ($C_{20}H_{12}N_2S_2$)
V : X: NH, A: H ($C_{20}H_{14}N_4$)

Figure 3. Mechanism of the synthesized symmetric bis-benzoxazole and their derivatives.

vibrations were not observed at the same place as bis-benzoxazole and its derivatives. Bands appeared at about 1600 and 1200 cm^{-1} in the benzoxazole and its other derivatives indicate that there are benzoxazole, bezthiazole and benzimidazole rings. These absorption data were in agreement with literature [4,20].

In the ^{1}H-NMR spectrum of compounds, CH aromatic peaks belonging to the *p*-phenylene ring in the centre of the compounds were observed between 8.38-8.30 ppm as a singlet while aromatic OH protons belonging to bisoxazol ring were observed between 8.21-7.16 ppm. Methyl protons in 5,5'-dimethyl-2,2'-(*p*-phenylenebenzoxazole) compound were observed at 2.48 ppm and NH protons in bis-(benzimidazole) compound were observed at 7.37 ppm as a singlet. ^{1}H-NMR values of these compounds are in good agreement with those of bis-benzoxazole and its derivatives [11,13].

The mass spectrums of the compounds show signals at 344 (m/z) and 345 (m/z) for compound IV, 340 (m/z) and

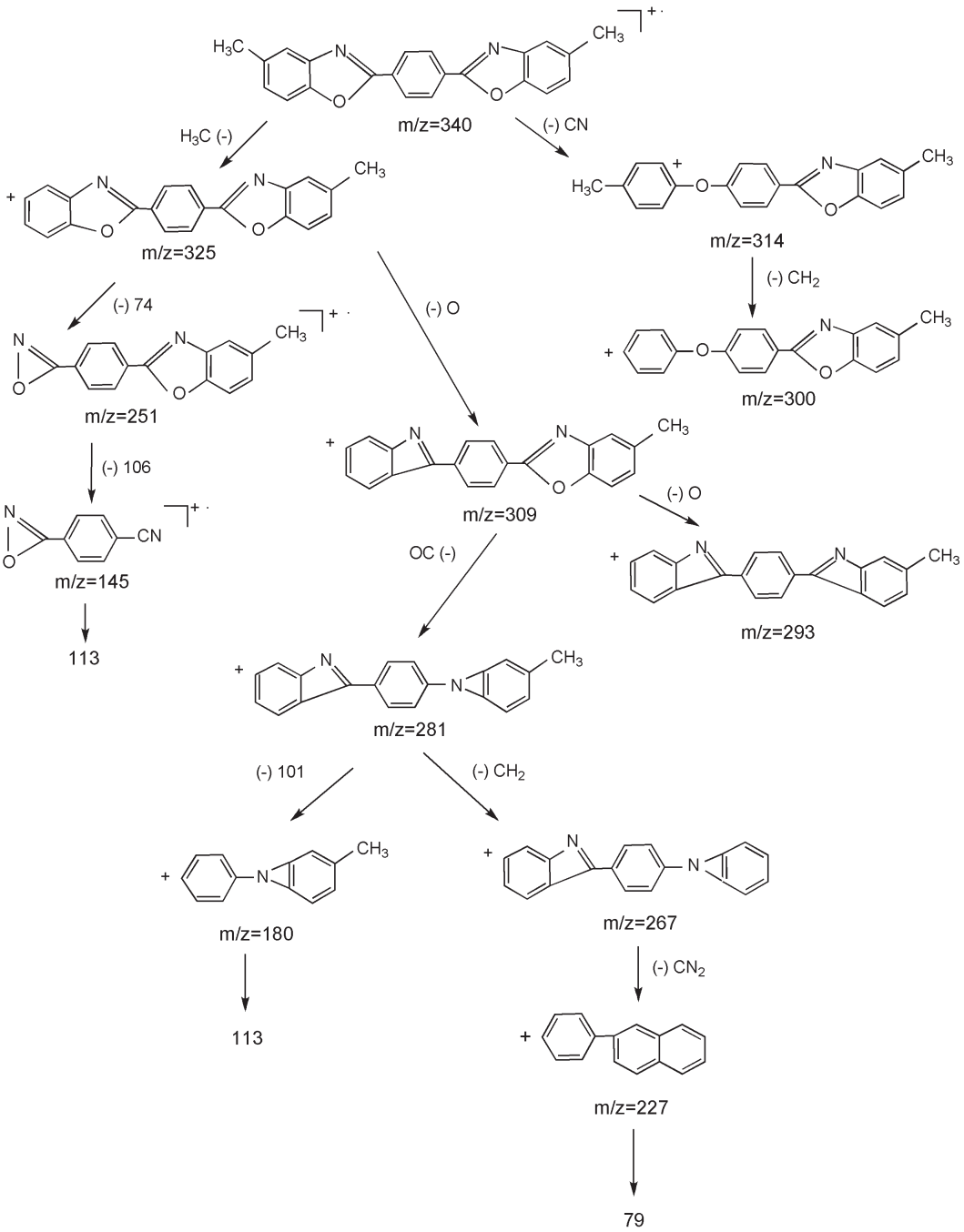


Figure 4. Proposed mass spectral fragmentation pattern of 5,5'-dimethyl-2,2'^{1}-(*p*-phenylene)bis(benzoxazole) (compound III)

341 (m/z) for compound III and 310 (m/z) and 311 (m/z) for compound V corresponding to their molecular and $(M+1)^+$ ion peaks, respectively. In the case of the compound IV, the $(M+2)^+$ peak is observed at 346 (m/z) due to the ^{34}S isotope indicating that compound IV contains a sulfur atom. Compound V shows a strong ion peak at 309 (m/z) which is attributed to $(M-H)^+$ ion. The proposed fragmentation pattern of compound III is given in Figure 4.

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