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Oxidation of Thiols to Disulfides (Polyphosphoric Acid method)

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ABSTRACT

During the synthesis of bis - benzothiazols via condensation of 2-aminothiophenol and oxalic, malonic acids an interesting product was obtained during the workup of the reaction products, which upon characterization by spectroscopic methods was found to be bis-(2-aminophenyl) disulfide ($NH_2PhSSPhNH_2$).

Introduction

Oxidation of thiols to the corresponding disulphide is a characteristic functional group transformation, in which further oxidation of the products to give disulphide S-oxides (thiosulphinates), disulphide S-dioxides (thiosulphonates) and sulphonic acids are possible, and consequently, considerable research has gone into controlling the initial oxidation. Disufide bond formation is a relevant transformation in many biological processes, since it is reversible for the construction of the secondary and tertiary structures in proteins, in addition, diaryl disulfide derivatives have often been employed as key intermediates in the synthesis of bioactive molecules due to the reversibility of S-S bond formation which allows them to participate in different exchange [1] and addition reactions [2]. Weak S-S bonds in the disulphide products leads to high reactivity[3] and in natural products, the presence of these moieties and related cyclic analogues are associated with interesting biological activities and DNA- cleaving properties[4]. The vital role of the thiols and disulphides in living systems is due to their interconversion reactions [5, 6]. Furthermore, this type of linkage is also of high value in industry. For instance, polysulfide bonds are present in well known useful polymers such as rubber, and compounds containing the disulfide moiety have proved suitable for the design of rechargable lithium battaries [7].

Several methods have been reported for the selective oxidative coupling of thioles [8-24], but most of the reported methods suffer from one or more disadvantages such as commercial unavailability, toxicity or high cost reagents, long reaction times, over- oxidation, unpleasant work-ups or the need to use halogenated or other environmentally unfriendly solvents. Most reagents used are metal based and toxic for the environment, while with others such as halogens (Br_2, I_2) and halogen containing reagents that are non-metallic, one encounters frequent difficulties in handiling the reagents and /or their seperation from the products. Herein we reported a new, easy and efficient method for oxidative coupling of thiols using polyphosphoric acid as oxidizing agent in the presence of dicarboxylic acid.

Results and discussion

Synthesis of the disulphide:

The compounds **1, 2, 3, 4 and 5** were synthesized according to Scheme 1 via the polyphosphoric acid method [25]. Condensation reactions of 2-aminothiophenol with oxalic, malonic, succinic and phthalic acids resulted in the formation of bis-(benzothiazol), 1,1-bis-(benzothiazolyl)methane, 1,2-bis-(benzothiazolyl) ethane , 1,2-bis-(benzothiazolyl) benzene and 2,6-bis-benzothiazolyl) pyridine respectively in addition to compound (1) bis(2-aminophenyl) disulfide . Depending on the acid used, the following reactions take place Scheme **1.**

In the presence of phthalic and succinic acids reaction 1 is favoured over reaction 2, while in case of oxalic acid the formation of disulfide (> 90%) is predomiante over the formation of Bis(benzimidazolyl) (*unpublished work*). Condensation of malonic acid and 2-aminothiophenol produces the two products 1,1-bis(benzothiazolyl)methane in 70% yield and disulphide in (30%) yield. The reasons for this rectivity difference might be accounted for from sterric point of view, since the yield of the benzimidazole compound is directly proportional to the length and rigidity of the bridging group i.e. when the bridging group is phenylene, pyridine and ethylene the yield of disulphide is nearly 0% while only 10% of bis-benzothiazolyl (entry 2 table 1) and 90% disulfide were obtained, methylene bridging group yields 30% disulphide and 70% 1,1-bis-(benzothiazolyl) methane. It is clear that the length of the bridge determine the reaction products keeping the other reaction condition the same.

The mechanism by which this reaction proceeds is not clear but we suggest that the reaction of polyphosphoric acid with dicarboxylic acid produces peroxycarboxylic acid Scheme 2. which oxidize the RSH to RSOH [13] .

This method offers a simple and efficient rout for the oxidation of thiols to the corresponding disulfides, and the disulfides did not undergo further oxidation to their crresponding disulfide –S- oxide (thiosulfinates), disulfide-S-

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dioxide (thiosulfonates), and /or sulfonic acids under the reaction conitions.

Characterization

^{1}H and ^{13}C NMR spectroscopy

The compounds **1-7** were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of **1** (Scheme 4) shows five sets of signals. The triplet at δ = 7.03 ppm [$J_{H,H}$ = 7.4 Hz] can be assigned to two aromatic protons (H4), the doublet at δ = 6.96 ppm [$J_{H,H}$ = 7.4 Hz] is assigned to two protons H3, and the doublet at δ = 6.68 ppm [$J_{H,H}$ = 7.4 Hz] can be assigned to H6. The triplet at δ = 6.38 ppm [$J_{H,H}$ = 7.4 Hz] corresponds to H5. At δ = 5.35 ppm the amino protons (H7) are located.

The ^{13}C NMR of compound **1** (Scheme 5) shows six signals, each signal is equivalent to two aromatic carbon atoms. The signal at δ = 150.7 ppm corresponds to C2, the signal at δ = 135.9 ppm is assigned to C4. The signal at δ = 132.0 ppm can be assigned to C1, the signal at δ = 117.1 ppm assigned to C5. Finally, the signals at δ = 116.9 and 115.1 ppm can be assigned to C6 and C3.

Mass spectroscopy

The mass spectrum of compound **1** (see Scheme x), shows the molecular ion peak at m/z = 248. the molecular ion peaks for compounds **2, 3, 4, 5, 6** and **7** (m/z) = 218, 246, 286 and 246 respectively.

Experimental

All experimental work was routinely carried out using Schlenk technique unless otherwise stated. Dried and purified argon was used as inert gas. n-Pentane, diethyl ether, toluene and tetrahydrofuran were purified by distillation over Na/K alloy. Diethyl ether was additionally distilled over lithium aluminum hydride. Methylene chloride was dried with phosphorus pentoxide and calcium hydride. Methanol and ethanol were dried over molecular sieves. Deuterated solvents ($CDCl_3$, DMSO) for NMR spectroscopy were stored over molecular sieves (3Å) and argon (4.8/5.0) were supplied by Rießner Company (Lichtenfels). All other starting materials were commercially available and were used without further purification.

NMR spectroscopy

The spectrometers Varian Inova 300/400 M Hz and Bruker ARX 250 were available for recording the NMR spectra. The samples were prepared under inert atmosphere (argon) and routinely recorded at 25 °C. The chemical shifts in the ^{1}H NMR spectra are referred to the residual proton signal of the solvent (δ = 7.24 ppm for $CDCl_3$, δ = 2.5 ppm for DMSO) and in ^{13}C NMR spectra to the solvent signal (δ = 77.0 ppm for $CDCl_3$, δ = 39.5 ppm for DMSO).

Mass spectrometry

Mass spectra were routinely recorded at the Zentrale Analytik of the University of Bayreuth with a VARIAN MAT CH-7 instrument (direct inlet, EI, E = 70 eV) and a VARIAN MAT 8500 spectrometer.

Elemental analysis

Elemental analyses were performed with a VarioEl III CHN instrument. Therefore 4-6 mg of the complex was weighed into a standard tin pan. The tin pan was carefully closed and introduced into the auto sampler of the instrument. The raw values of the carbon, hydrogen, and nitrogen contents were multiplied with calibration factors (calibration compound: acetamide).

Synthesis of bis-(2-aminophenyl)disulfide 1and bis-benzimidazoles (2-7)

2-aminothiophenol (0.05mol) was mixed with a dicarboxylic acid or an acid anhydride (0.025mol) and the mixture was poured in 50 ml of preheated (100°C) polyphosphoric acid. The mixture was stirred and heated at 175°C for 3-5 hours. The reaction mixture was then poured in ice cold water and allowed to stand overnight. The precipitate was removed by filtration and washed several times with diluted sodium hydrogen carbonate solution and finally with water. The reaction product was then air dried and weighed (Bis-benzothiazole 2-7) table 1. The mother liquor was allowed to stand overnight a yellow crystalline preciptate was formed filtered, washed with water, air dried and characterized by NMR) mass spectroscopy (Table 1) and elemental analysis (Table 2).

Conclusions:

A facile and efficient method for the synthesis of symmetric disulfide was described using polyphosphoric acid as oxidant and solvent in the presence of dicarboxylic acid(oxalic and malonic) acids. Several advantages of this method which include high yields of product, ease of isolation and use of non-toxic and cheep oxidant which makes this reaction convenient and efficient.

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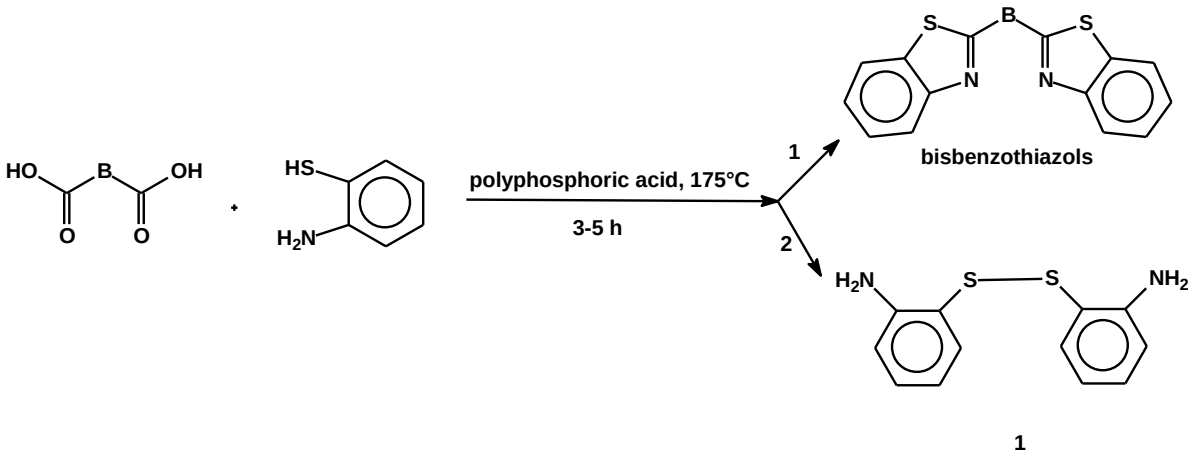
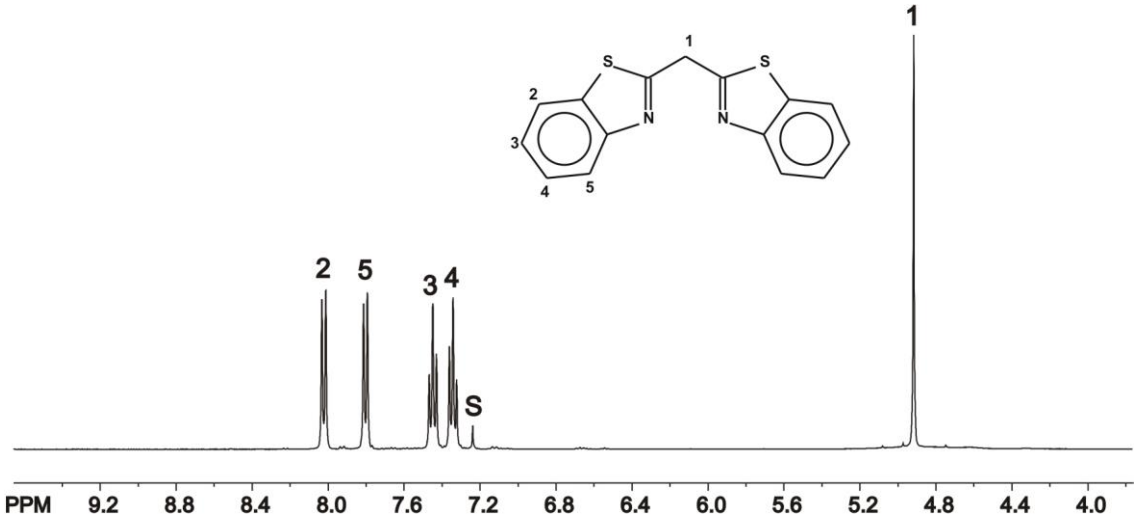
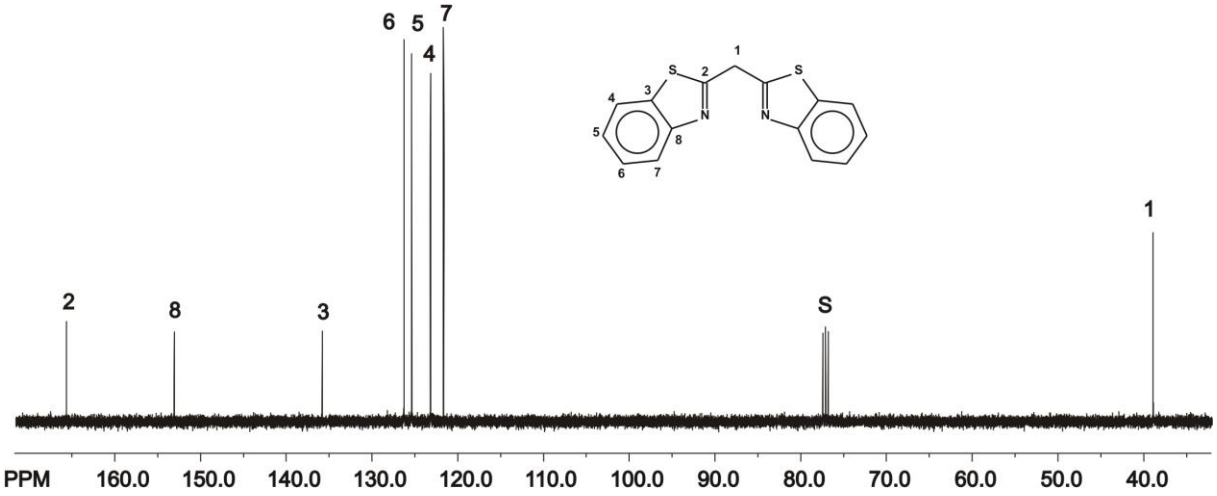


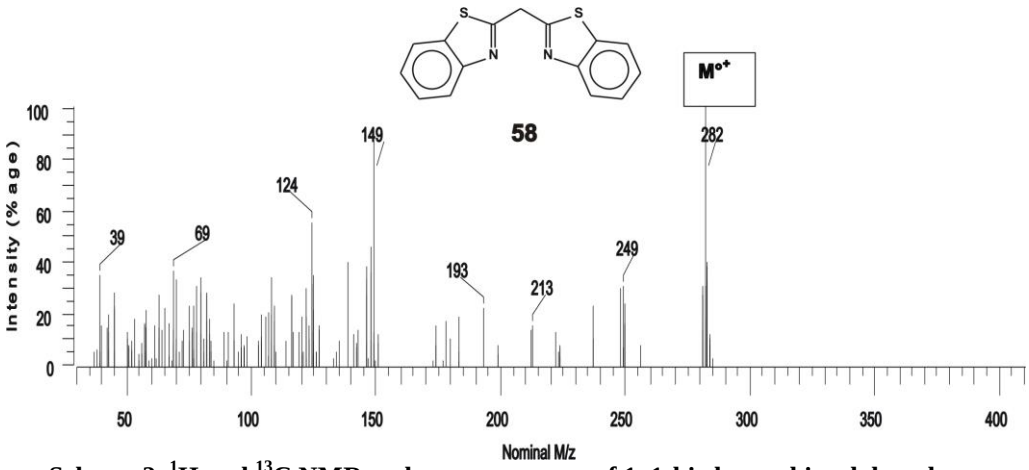
1

B = 0, methylene, ethylene, phenylene, methyl phenylene, pyridine

Scheme 1. Synthesis of disulfides (1) and bis-benzothiazolyl compounds (2-7)

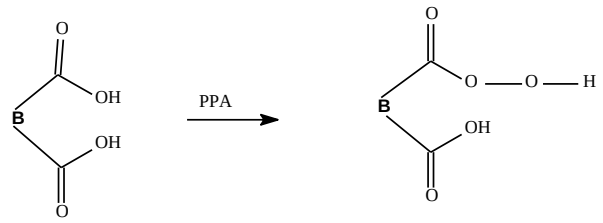




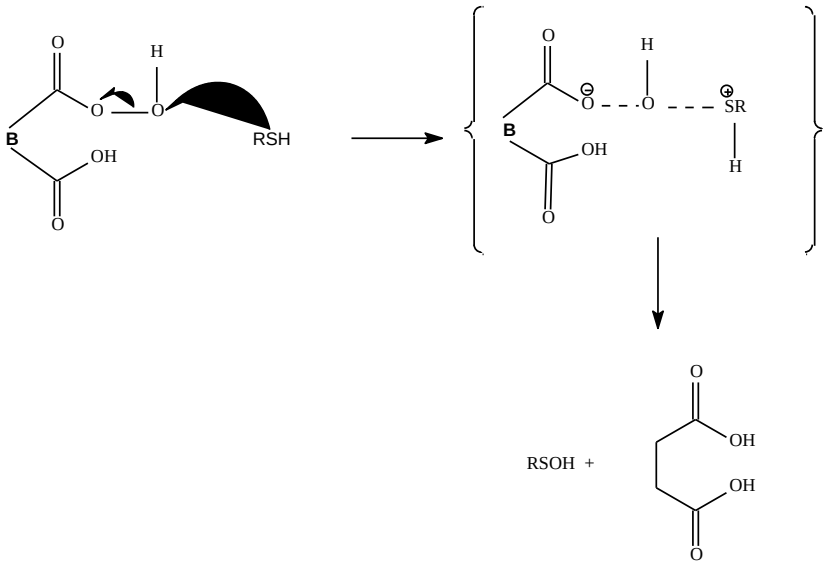


Scheme 2. ^{1}H and ^{13}C NMR and mass spectrum of 1, 1-bis-benzothiazolyl methane

1)



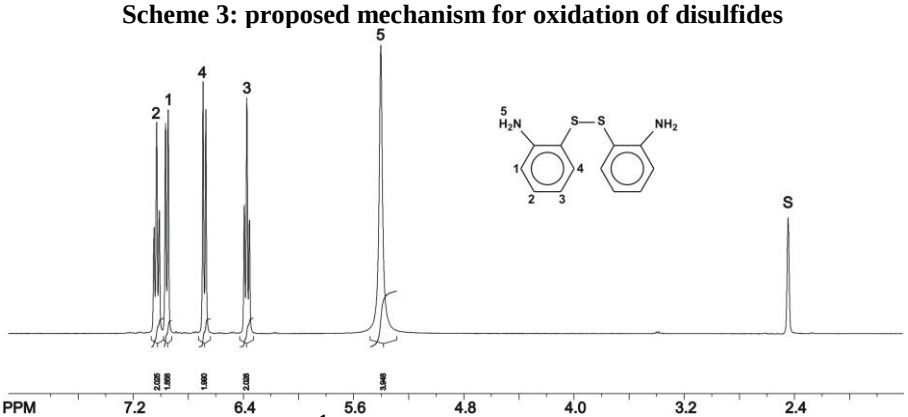
2)



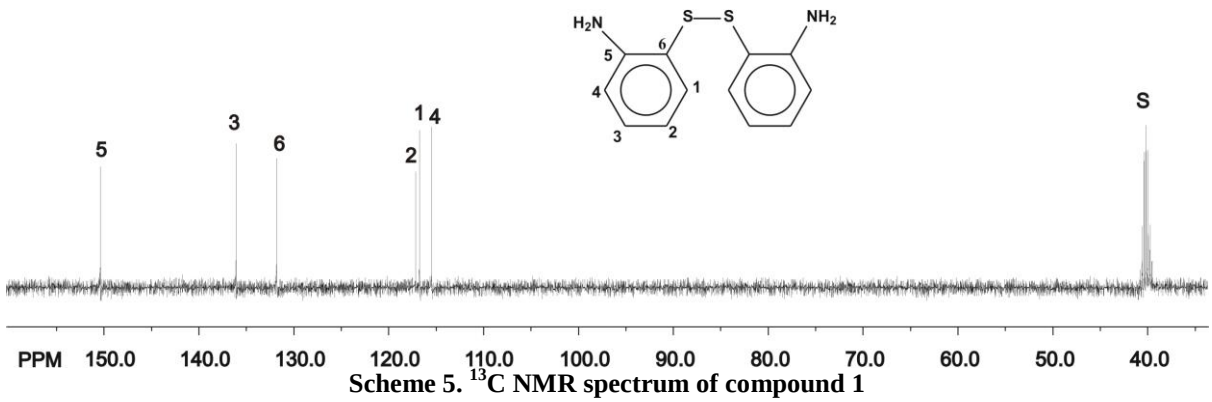
3)

$$RSH + RSOH \longrightarrow RSSR + H_2O$$

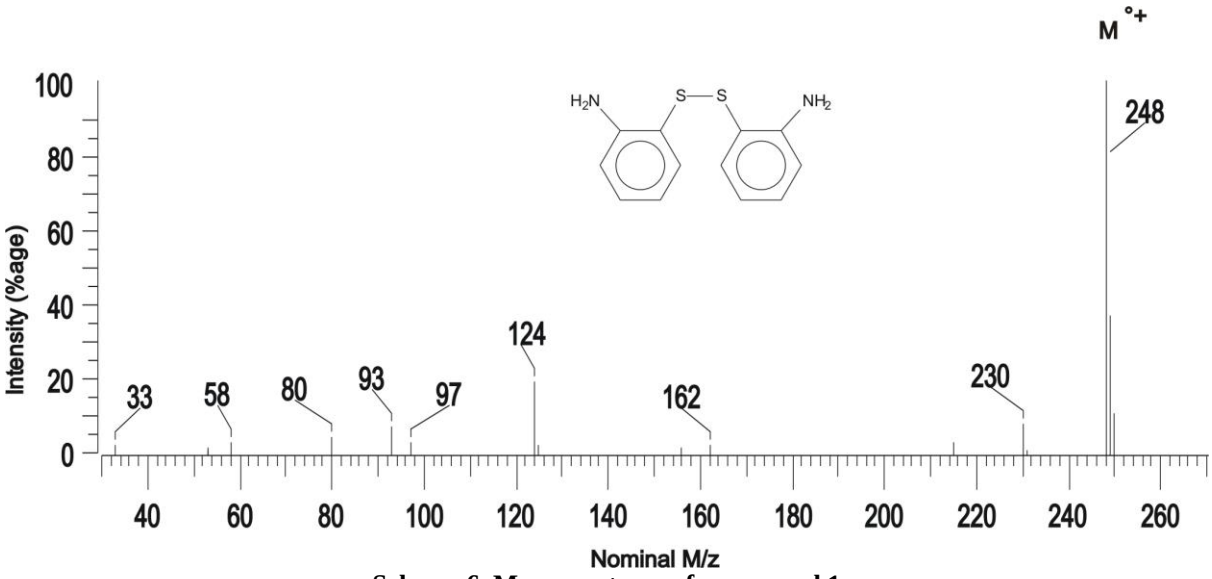
Scheme 3: proposed mechanism for oxidation of disulfides



Scheme 4. ^{1}H NMR spectrum of compound 1



Scheme 5. ^{13}C NMR spectrum of compound 1



Scheme 6. Mass spectrum of compound 1

Table 1. ^{1}H, ^{13}C NMR and mass spetra

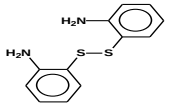
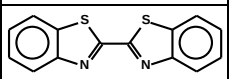
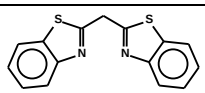
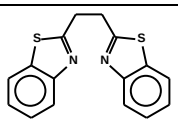
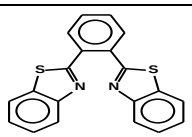
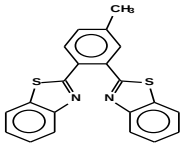
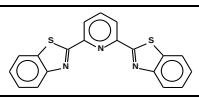
No	Thiol	^{1}HNMR δ ppm	^{13}CNMR δ ppm	Mass
1		7.03 (t, H), 6.96 (d,2H), 6.68 (d,2H), 6.38 (t,2H) , 5.35 (s,4H, 2NH_2)	150.7 135.9, 132.0, 117.1, 116.9, 115.1	248 $M^{\circ+}$ (100)
2		8.15(d,2H), 7.96(d,2H), 7.54(t,2H), 7.47(t,2H)	n.d.	268 $M^{\circ+}$ (100)
3		8.04(d,2H), 7.95(d,2H), 7.47(t,2H), 7.43(t,2H), 5.05(s,2H,CH_2)	167.0, 153.2, 135.9, 127.0, 125.9, 123.2, 122.9, 38.5	282 $M^{\circ+}$ (100)
4		7.98(d,2H), 7.82(d,2H), 7.44(t,2H), 7.37(t,2H), 3.74(s,4H, 2CH_2)	169.6, 153.5, 135.5, 126.4, 125.3, 123.0, 121.9, 33.6	296 $M^{\circ+}$ (100)
5		8.01(d,2H), 7.93-7.90(dd,2H), 7.77(d,2H), 7.61-7.58(dd,2H), 7.44(t,2H), 7.33(t,2H)	166.4, 153.4, 136.6, 133.5, 131.6, 131.5, 127.2, 126.3, 123.8, 121.9	344 $M^{\circ+}$ (100)
6		8.01-7.95(m,2H), 7.84-7.79(m,3H), 7.74(s,1H), 7.48-7.44(m,3H), 7.38-7.33(m,2H), 2.50(s,3H, CH_3)	166.6, 166.5, 153.6, 153.5, 141.1, 136.8, 136.8, 133.5, 131.8, 131.2, 131.1, 131.0, 126.3, 126.2, 125.5, 125.4, 123.6, 123.5, 121.7, 121.6, 21.3	358 $M^{\circ+}$ (100)
7		8.41(d,2H), 8.09(d,2H), 8.00-7.95(m,3H), 7.51(t,2H), 7.42(t,2H)	168.8, 154.5, 151.5, 138.4, 136.6, 126.6, 126.15, 124.0, 122.2, 122.1	345 $M^{\circ+}$ (100)

Table 2. Elemental analysis (CHN)

Compound No.	Calculated			Found		
	C	H	N	C	H	N
1	58.06	4.84	11.29	58.10	4.83	11.27
2	62.69	2.99	10.44	62.70	3.01	10.46
3	63.83	3.55	9.93	63.82	3.57	9.92
4	64.86	4.05	9.46	64.88	4.03	9.44
5	69.77	3.49	8.14	69.75	3.51	8.16
6	70.39	3.91	7.82	70.40	3.92	7.81
7	66.09	3.19	12.17	66.11	3.20	12.16

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