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Synthesis and Spectral Analysis of 3,4,5-trichloro-6-(dibenzo[*d,f*][1,3]diazepin-5-yl)-[1,2]-benzoquinones

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Abstract: Reaction of N^1,N^2-di-(4-methoxyphenyl)- or N^1,N^2-di-(4-hydroxyphenyl) -amidines (**1a-d)** with 3,4,5,6-tetrachloro-1,2-benzoquinone (**2**) in ethyl acetate at room temperature led to formation of new 3,4,5-trichloro-6-(2-hydroxy-6-methyldibenzo[*d,f*][1,3]diazepin-5-yl[1,2]-benzoquinones (**3a-d**) in addition to *N*-aryl-*N′*-(6,7,8,9-tetrachloro-4-hydroxydibenzo-[1,4]dioxin-2-yl)acetamidines (**4a,b)**. The rational of formation of products **3a-d** and **4a,b** was discussed and structures were confirmed on the basis of elemental analysis and spectral data.

Keywords: Diazepine, Amidine, Benzoquinone, Dibenzodioxine, Dioxines

Introduction

Amidines find widespread application in organic chemistry as starting materials for preparation of many different nitrogen-containing heterocycles[1]. Early we reported on the reaction of N^1,N^2-diarylamidines with 2,3,5,6-tetrachloro-1,4-benzoquinone and isolation of tetrahydroindolones[2]. Later we reported a synthesis of 1,11b-dihydrodibenzodiazepine-1(5*H*)-ones from the reaction of the nitro-substituted N^1,N^2-diarylamidines with 3,4,5,6-tetrachloro-1,2-benzoquinone (**2**)[3]. In contrast, in the reaction of N^1,N^2-diphenyl- or di-(4-*tert*-butylphenyl)amidines with **2**, 6,7,8,9-tetrachlorodibenzodioxines were obtained *via* a formal [4+2] cycloaddition reaction[3]. 3,4,5,6-Tetrachloro-1,2-benzoquinone often reacts as a diene at C3, C6 with dienophiles through [4+2]-cycloaddition, or as a 1,2-dione type heterodyne giving rise to either bicyclic 1,2-diones (with *e.g.* alkynes[4] and with 1,2-bisimines to form bicyclic iminoketones finally[5].

When double bond dienophiles are used the cycloaddition is followed by a dehydrogenation of the primary adducts to form fused dioxins[6–8]. Alternatively this quinone may undergo nucleophilic attack by *e.g.* the *N*-atoms of *N,N′*-dibenzylidene ethylenediamine at both carbonyl groups and at the chlorine atoms followed by condensation (elimination of

either H_2O or HCl)[9]. Later we have synthesized various 4-aryl-5-imino-3-phenyl-1*H*-naphtho[2,3-*f*]-1,2,4-triazepine-6,11-diones *via* reaction of amidrazones with 1,4-dioxo-1, 4-dihydronaphthalene-2,3-dicarbonitrile[10]. Also we have succeeded to synthesize various benzo- and naphtho-1,2,4-triazin-6-ones via the reaction of amidrazones with benzo- and naphtho 1,4-quinones, while reaction of amidrazones with 2,3,5,6-tetrachloro-1, 4-benzoquinone or 2,3-dichloro-1,4-naphthoquinone led to formation of indazoles[11]. This prompted us to investigate reactions of different substituted N^1,N^2-diarylamidines with 3,4,5,6-tetrachloro-1,2-benzoquinone (**2**).

Experimental

The uncorrected melting points were determined on a Gallenkamp apparatus. Elemental analyses were obtained on a Carlo Erba 1106 CHN analyzer, while the IR (potassium bromide) were recorded on a Schimadzu 470 spectrophotometer. The 300 MHz ^{1}H and 75 MHz ^{13}C nmr spectra were observed on a Bruker WM 300 instrument with TMS as the internal standard using dimethylsulfoxide-d_6 as solvent. The ^{13}C signals were assigned on the basis of DEPT 135/90 spectra. The mass spectra (70 eV, electron impact mode) were recorded on AMD 604 instrument. Preparative layer chromatography (plc) used air dried 1.0 mm thick layers of slurry applied silica gel Merck PF_{254} on 48 cm wide and 20 cm high glass plates and toluene-ethyl acetate (10:1) as developing solvent. Zones were detected by quenching of indicator fluorescence upon exposure to 254 nm light and eluted with acetone or ethyl acetate.

Starting materials

3,4,5,6-Tetrachloro-1,2-benzoquinione (**2**) was used as received from Aldrich. N^1,N^2-Diarylamidines (**1a-d)** were prepared according to literature procedures[12].

General procedure for preparation of **3a-d** *and* **4a,b**

To a solution of amidines **1a-d** (1.0 mmol) in ethyl acetate, 2.0 mmol of *o*-chloranil (**2)** in ethyl acetate was added and left at room temperature in stirring overnight. The solution was concentrated and subjected to plc using toluene/ethyl acetate 2:1 as developing solvent. Two zones were extracted the faster moving contained compound **4a** or **4b**, while the second contained compound **3a, 3b, 3c** or **3d**.

3,4,5-Trichloro-6-(2-hydroxy-10-methoxy-6-methyl-dibenzo[d,f][1,3]diazepin-5-yl) benzo-1,2-quinone **(3a)**

Yield 0.29 g (63%). –M.p. 239-240 °C; as orange crystals (ethyl acetate). -IR (KBr) ν = 3300 (OH), 1679 (CO) and 1640 (CO) cm^{-1}. – 1H NMR (300 MHz, d_6-DMSO): δ = 1.85 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 6.47 (d, 1H, $|^4J|$ = 1.88, Hz, 1-H), 6.85 (d, 1H, ^3J = 9.0 Hz, 4-H), 6.90 (d,d, 1H, ^3J = 9.0 Hz, ^4J = 1.88 Hz, 3-H), 6.94 (d, 1H, ^3J = 8.92 Hz, 8-H), 7.23 (d, 1H, $|^3J|$ = 8.94 Hz, 9-H), 7.53 (d, 1H $|^4J|$ = 1.9 Hz 11-H), 7.59 (s, 1H, OH). –^{13}C{^{1}H} NMR (75 MHz, d_6-DMSO): δ = 21.84 (CH_3), 55.31(OCH_3), 106.80, 113.63, 127.82, 135.19, 135.30, 135.84 (aryl CH), 113.70, 120.05, 128.31, 130.75, 133.37, 140.51, 148.85, 157.29, 169.26, 170.42, 185.74, 185.85. –MS (EI, 70 eV): *m/z* (%) = 464 (40) [M$^+$], 420 (100), 407 (54), 350 (19), 248 (32), 210 (22), 148 (29), 108 (16), 77 (8), 44 (66). -$C_{21}H_{13}Cl_3N_2O_4$ (464.86): calcd. C, 54.38; H, 2.83; N, 6.04; found: C, 54.24; H, 2.86; N, 6.08.

3,4,5-Trichloro-6-(6-ethyl-2-hydroxy-10-methoxy-dibenzo[d,f][1,3]diazepin-5-yl) benzo-1,2-quinone **(3b)**

Yield 0.25 g (52%). –M.p. 210-212 °C; as orange crystals (ethyl acetate). -IR (KBr) ν = 3400 (OH), 1676 (CO) and 1642 (CO) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, 3H, $|^{3}J|$ = 7.43 Hz, Me), 2.49 (q, 2H, $|^{3}J|$ = 7.43 Hz, $\underline{CH_2}Me$), 3.80 (s, 3H, OCH_3), 6.42-7.36 (s, 1H, OH), 7.65 several m (6H, aryl -H). – $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ = 9.31 (CH_3), 27.44 (CH_2), 55.43 (OCH_3), 108.19, 114.58, 128.39, 134.71, 136.11, 136.52 (aryl CH), 114.08, 121.44, 130.36, 133.54, 136.26, 138.79, 140.21, 147.95, 158.30, 175.15, 185.15, 185.97. –MS (EI, 70 eV): *m/z* (%) = 478 (36), [M^+], 422 (100), 405 (31), 389 (15), 350 (10), 57 (16). – $C_{22}H_{15}Cl_3N_2O_4$ (478.86): calcd. C, 55.29; H, 3.16; N, 5.86; found: C, 55.18; H, 3.12; N, 5.79.

3,4,5-Trichloro-6-(2,10-dihydroxy-6-methyl-dibenzo[d,f][1,3]diazepin-5-yl)benzo-1,2-quinone (**3c**)

Yield 0.24 g (53%). –M.p. 360 °C; as orange crystals (ethyl acetate). -IR (KBr) ν = 3450 (OH); 1643 and 1625 (CO) cm^{-1}. –^{1}H NMR (300 MHz, d_6-DMSO): δ = 1.97 (s, 3H, Me), 6.40 (d, 1H, ^{4}J = 1.81 Hz, 1-H), 6.67 (d, 1H, ^{3}J = 8.78 Hz, 4-H), 6.89 (d,d, 1H, ^{3}J = 9.82 Hz, ^{4}J = 1.11 Hz, 3-H), 7.10 (d, 1H, ^{3}J = 8.80 Hz, 8-H), 7.41 (d, 1H, ^{3}J = 8.73 Hz, 9-H), 7.60 (d, 1H, $|^{4}J|$ = = 1.93 Hz, 11-H), 7.65 (br, 2H, OH). –$^{13}C\{^{1}H\}$ NMR (75 MHz, d_6-DMSO): δ = 22.04 (CH_3), 106.79, 115.06, 128.19 , 135.43, , 135.98, 136.04 (aryl-CH), 120.06, 130.88, 133.77, 135.41, 138.79, 140.64, 148.70, 149.10, 151.14, 157.24, 169.47, 170.97, 186.04. –MS (EI, 70 eV): *m/z* (%) = 450 (17), [M^+], 448 (14), 408 (55), 336 (25), 43 (65), 36 (100). – $C_{20}H_{11}Cl_3N_2O_4$ (450.83): calcd. C, 53.42; H, 2.47; N, 6.23; found C, 53.40; H, 2.41; N, 6.19.

3,4,5-Trichloro-6-(6-ethyl-2,10-dihydroxy-dibenzo[d,f][1,3]diazepin-5-yl)benzo-1, 2-quinone (**3d**)

Yield 0.30 g (65%). –M.p. 360 °C; as reddish brown crystals (ethanol). -IR (KBr) ν = 3450 3223 (OH); 1637 and 1621 (CO) cm^{-1}. –^{1}H NMR (300 MHz, d_6-DMSO): δ = 1.02 (t, 3H, ^{3}J = 7.31 Hz, Me), 2.35 (d, 2H, ^{3}J = 7.40 Hz, $\underline{CH_2}Me$), 6.40, (d, 1H, ^{4}J = 1.82 Hz, 1-H), 6.76 (d, 1H, ^{3}J = 8.72 Hz, 4-H), 6.92 (d,d, 1H, ^{3}J = 9.83 Hz, ^{4}J = 1.82 Hz, 3-H), 7.09, (d, 1H, ^{3}J = 8.76 Hz, 8-H), 7.41 (d, 1H, ^{3}J = 8.76 Hz, 9-H), 7.59 (d, 1H, ^{3}J = 1.8 Hz, 11-H), 7.63 (br, 1H, Hz, OH). –$^{13}C\{^{1}H\}$ NMR (75 MHz, d_6-DMSO): δ = 9.55 (Me), 27.71 ($\underline{CH_2}Me$), 106.81, 115.10, 128.28, 135.46, 136.01, 136.09 (aryl-CH), 119.98, 128.44, 130.87, 132.10, 133.81, 140.64, 148.79, 150.28, 155.81, 172.84, 174.22, 186.06 – MS (EI, 70 eV): *m/z* (%) = 464 (21) [M^+], 462 (18), 409 (41), 408 (100), 406 (88), 389 (17), 336 (27), 57 (81), 44 (48). – $C_{21}H_{13}Cl_3N_2O_4$ (464.83): calcd: C, 54.39; H, N, 2.83; found C, 54.49; H, 2.81; N, 5.90.

N-(*4-Methoxyphenyl*)-*N'-(6,7,8,9-tetrachloro-4-hydroxydibenzo[1,4]dioxin-2-yl) acet-amidine* (**4a**)

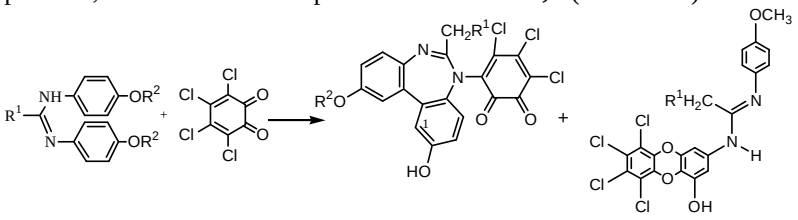
Yield 0.1 g (20%). –M.p. 256-258 °C; as brown crystals (ethyl acetate/cyclohexane). -IR (KBr) ν = 3400 (OH), 3262 (NH) and 1665 (C=N) cm^{-1}. –^{1}H NMR (300 MHz, d_6-DMSO): δ = 2.08 (s, 3H, CH_3), 3.70, (s, 3H, OCH_3), 6.64- 7.56 several m (6H, Ar-H), 8.14 (br, 2H, NH and OH). –$^{13}C\{^{1}H\}$ NMR (75 MHz, d_6-DMSO): δ = 22.06, (CH_3), 55.39 (OCH_3), 106.32, 113.76, 128.13, 132.44, (aryl CH), 120.30, 128.88, 130.92, 133.37, 134.16, 137.71, 140.86, 148.70, 149.19, 157.49, 158.81 (quart. C). –MS (EI, 70 eV): *m/z* (%) = 498 (41) [M^+], (M^+, 41), 456 (100), 441(43), 424 (26), 384 (11), 210 (13), 148 (32), 123 (17), 43 (23). – $C_{21}H_{12}Cl_4N_2O_4$ (498.35): calcd. C, 50.61; H, 2.43; N, 5.62; found: C, 50.69; H, 2.37; N, 5.54.

N-(4-*Methoxyphenyl*)-*N'-(6,7,8,9-tetrachloro-4-hydroxydibenzo[1,4]dioxin-2-yl) propion-amidine* (**4b**).

Yield 0.13 g (25%). –M.p. 229-230 °C; as brown crystals (ethyl acetate/cyclohexane). -IR (KBr) ν = 3390 (OH), 3148 (NH) and 1643 (C=N) cm^{-1}. $-^1H$ NMR (300 MHz, $CDCl_3$): δ =1.18, (t, 3H, $|^3J|$ = 7.42 Hz, Me), 1.59 (br, 1H, NH or OH). 2.43 (q, 2H, $|^3J|$ = 7.42 Hz, $\underline{CH_2}Me$), 3.77, (s, 3H, OCH_3), 6.58 (s, 1H, Ar-H), 6.89 -7.48 several m (4H, Ar-H), 7.70 (s, 1H, Ar-H), 7.75(s, 1H, NH or OH). $-^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 9.33, (Me), 27.45, ($\underline{CH_2}Me$), 55.45, (OMe), 107.69, 114.66, 129.80, 131.59 (aryl CH), 121.62, 130.82, 133.68, 136.76, 138.86, 139.85, 142.32, 147.91, 148.57, 149.09, 159.44 (quart. C);. –MS (EI, 70 eV): *m/z* (%) = 512 (34) [M^+], 456, 441, 426, 350, 57, 44. $-C_{22}H_{14}Cl_4N_2O_4$ (512.35): C, 51.57; H, 2.75; N, 5.47; found: C, 51.52; H, 2.69; N, 5.41.

Results and Discussion

Addition of an ethyl acetate solution of 3,4,5,6-tetrachloro-1,2-benzoquinone (*o*-chloranil) (**2**) to solutions of amidines (**1a-d)** in the same solvent resulted, after standing overnight at room temperature, in the formation of products **3a-d** and **4a,b** (Scheme 1.).



1a-d **2** **3a-d** **4a,b**

1,3,4	a	b	c	d
R^1	H	CH_3	H	CH_3
R^2	CH_3	CH_3	H	H

Scheme 1

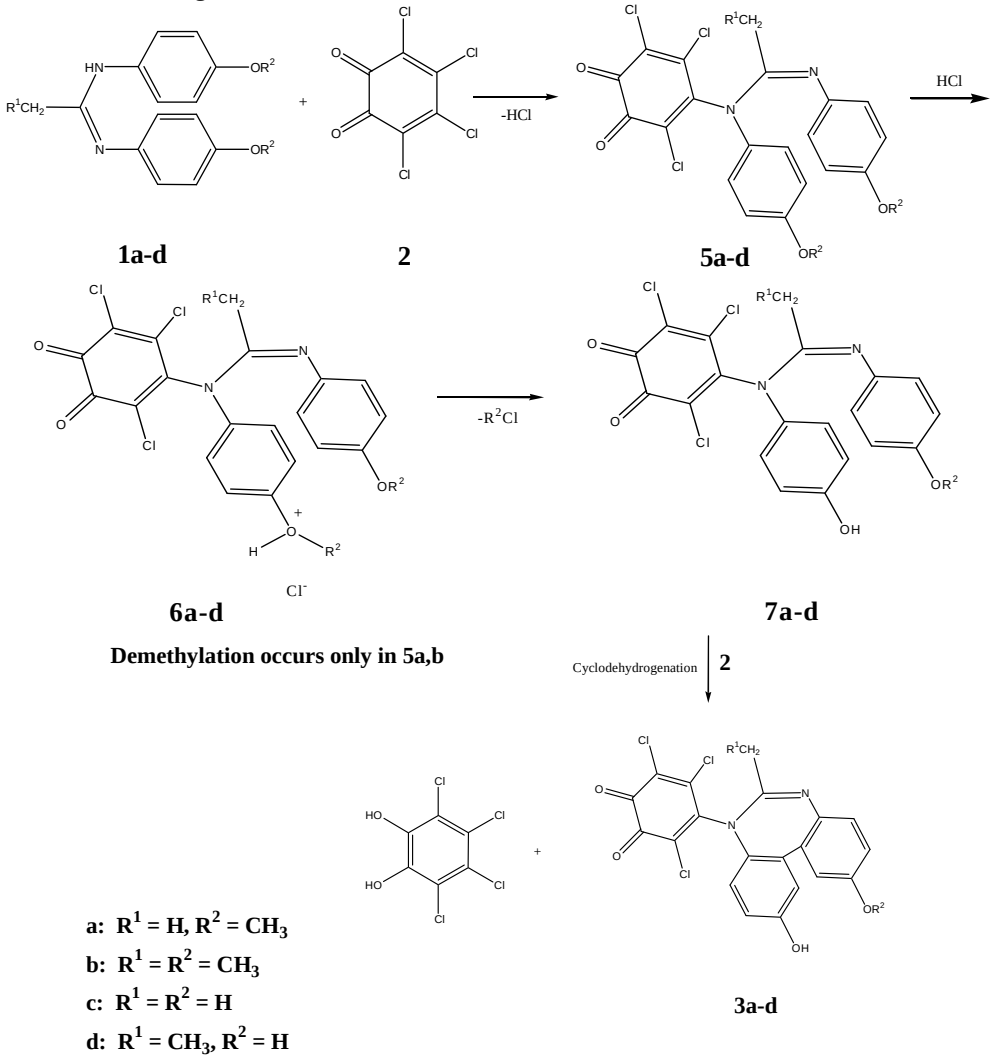
*The structural assignment of products **3a-d** is based on the following data*

Mass spectra of **3a-d** revealed that the products are 1:1 substitution products formed by release of HCl followed by demethylation (in the case of **1a,b**) and finally cyclodehydrogenation processes. For example ^{13}C NMR spectrum of **3b** showed 21 signals, six signals for aromatic CH, three signals at higher field identified as methyl, methylene and methoxy carbon atoms and fourteen quaternary carbon atoms, three of them resonating at downfield at δ = 185.15, 185.97 ppm for the two carbonyl carbon atoms. ^{13}C DEPT spectrum of **3b** showed a signal with a negative amplitude at 27.44 ppm was assigned to the exo methylene carbon atom, for more details see the experimental section. ^1H NMR spectrum of **3b** showed an OH proton and only six aromatic protons and only one methoxy group indicating a release of methyl group as CH_3Cl. The elemental analyses supported the compositions assigned and the mass spectra showed the molecular ion as 3Cl-atom clusters demonstrating that substitution of one chlorine atom had occurred.

The rationale for the formation of **3a-3d** can be described as follows: The reaction proceeds through a nucleophiliuc substitution with liberation of HCl which serves as a demethylating agent (only for **5a,b**) for one of the two methoxy groups. Thereafter the *o*-chloranil **2** dehydrogenates the intermediates **7a-d** to give ultimately dibenzodiazepine derivatives **3a-d** (Scheme 2). *o*-Chloranil is usually used as an oxidizing agent[3]. so it is not surprising to behave as an electrophile as well as a dehydrogenating agent. Recently it was reported that treatment of substituted

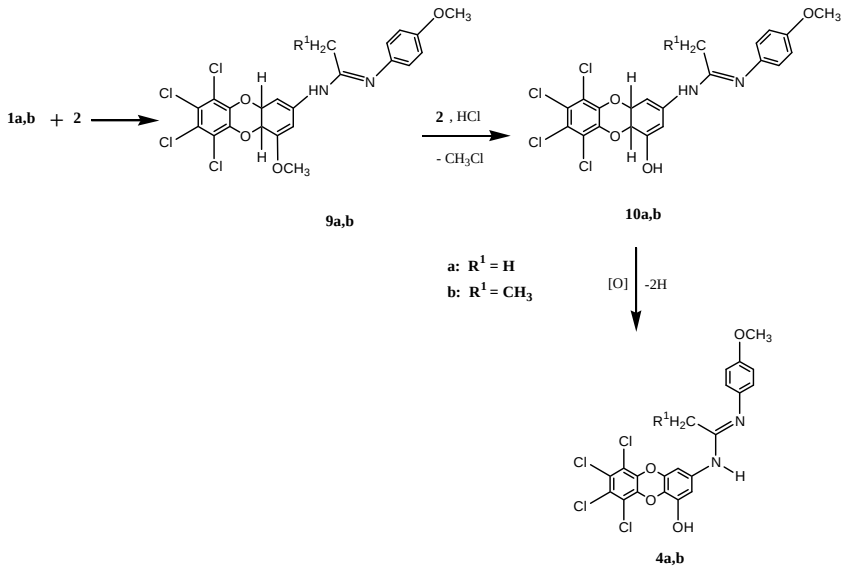
4-methoxyanilines with ceric ammonium nitrate CAN in acetonitrile resulted in the formation of 1,4-benzoquinones in acceptable yields[13]. But in this present investigation the *o*-chloranil is not strong oxdizing agent like CAN, it can be considered as a mild oxdiznig agent[14].

These results open a satisfactory route to dibenzodiazepines **3a–d** in good yield (52-65%). Diazepines are a class of heterocycles with potential pharmacological interest[15]. At present, we do not have a satisfactory explanation for the formation of only one product (**3c,d**) in the reaction of N^1, N^2-di-(4-hydroxyphenyl)amidines **1c,d** with **2**; it is probably due to the higher nucleophilicity of the N^1, N^2-di-(4-methoxyphenyl)amidines **1a,b** compared with their homologues **1c,d**.



Scheme 2

While the formation of **4a,b** may be rationalized as follows: **1a,b** reacts with **2** via a formal [4+2]- cycloaddition reaction[3,6-8] to afford the intermediate **9a,b** which undergoes demethylation and dehydrogenation to give finally **4a,b** (Scheme 3).



Scheme 3

Conclusion

In summary this study shows that the mild conditions in the reaction of N^1, N^2-dimethoxy- or dihydroxyphenylamidines with a 3,4,5,6-tetrachloro-1,2-benzoquinone can be used for the synthesis of new 3,4,5-trichloro-6-(dibenzo[*d,f*][1,3]diazepin-5-yl)-[1,2]-benzoquinones.

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