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OXIDATIVE COUPLING OF 4,5,6-TRICHLOROGUAIACOL WITH IRON(III) HEXACYANOFERRATE(III)

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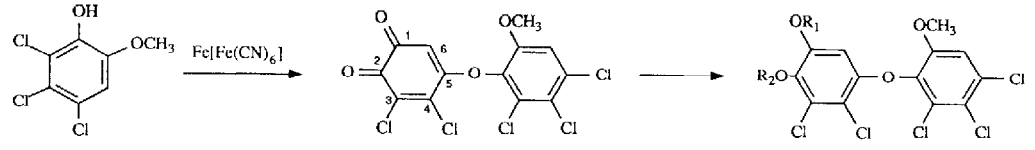
Iron(III) hexacyanoferrate(III) is shown to be a useful reagent in oxidative coupling of 4,5,6-trichloroguaiacol (4,5,6-TCG). Dimerisation proceeds via oxidative demethylation and loss of chloride to give an *ortho*-quinonoid dimer in high yield. The proposed structure **1** is based largely on mass-spectra of methyl derivatives of the corresponding diol.

Iron(III) hexacyanoferrate(III) *(1)* has been used as a one-electron reagent to effect intramolecular carbon-carbon and carbon-oxygen coupling of bifunctional β-dicarbonyl compounds *(2)*. The present study was initiated to investigate the usefulness of this complex for dimerisation of chlorinated guaiacols, not reactive to iron(III)-ions or potassium hexacyanoferrate(III) alone. 4,5,6-TCG, of environmental importance through its occurence in bleached kraft mill effluents *(3)*, was chosen as a model compound.



4,5,6-TCG

1

2 $R_1=R_2=H$ 4 $R_1=CH_3$ $R_2=H$
3 $R_1=R_2=CH_3$ 5 $R_1=H$ $R_2=CH_3$

Scheme 1.

SYNTHESIS

To an aqueous solution of 4,5,6-TCG *(4)*, the oxidation agent iron(III) hexacyanoferrate(III) is added as a freshly made 0.18 M solution *(5)* in a 5-fold molar excess. After stirring for 15 min at room temperature the oxidation is stopped by adding potassium fluoride *(6)*. This prevents the potassium iron(III) hexacyanoferrat(II), also known as Prussian Blue, from precipitating and thus interfering with the isolation of the main product which precipitated from the solution as a yellow microcrystallisate. It was conveniently isolated by extraction with dichloromethane. The oxidation

gives >90% yield of 3,4-dichloro-5-[2',3',4'-trichloro-6'-methoxy-phenoxy]-cyclohexa-3,5-dien-1,2-dione **1** *(7)* and traces of a hitherto unidentified by-product, so far only characterised on TLC *(8)*. Reduction of **1** with ascorbic acid *(9)* gives 2,3,4,2',3'-pentachloro-4',5'-dihydroxy-6-methoxy-diphenyl ether **2** *(10)* which upon subsequent methylation with diazomethane gives 2,3,4,2',3'-pentachloro-4',5',6-trimethoxydiphenyl ether **3** *(11)*, characterized by GC-MS (Table 1). No isomers of **3** could be detected on GC-ECD *(12)* after methylation of crude **2** obtained from unpurified **1**.

Two partially methylated products **4** and **5** were obtained through short methylation of **2** with diazomethane, and characterized by GC-MS.(Table 1)

Table 1. GC retention times and selected fragments of mono- and dimethylderivatives of **2** on GC-EIMS*. Calculations based upon fragments containing ^{35}Cl only.

	ret.time (min)	m/e	M^+	$[M-15]^+$	$[M-50]^+$	$[M-70]^+$
3	27.1	430	100	78	<5	<5
4	28.5	416	100	11	12	38
5	28.1	416	85	100	<5	5

* GC-MS analyses were performed on a Finnigan 4021 instrument, ion source temperature 140°C, electron energy 70eV: GC separations were performed on a fused silica capillary column DB-5 30m x 0.25mm, film thickness 0.025mm (J&W Scientific, Inc., CA, USA).
Temperature program 80°C/2min-10°C/min-280°C/20min.

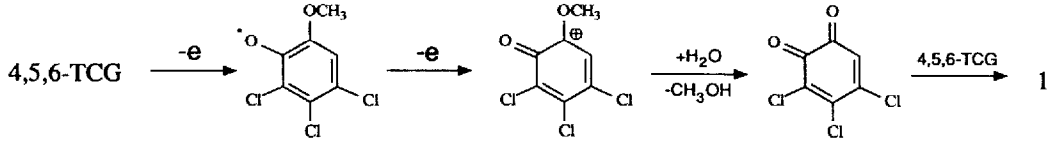
DISCUSSION

The proposed structures of **1-5** which presume coupling in position 5 (scheme 1) of the quinonoid part of the dimer are based on fragmentation patterns on GC-MS (electron impact) of **3, 4** and **5**. According to Tulp and Hutzinger and Humppi *et al. (13)* the position of the methoxy-group of a methoxy-polychlorodiphenyl ether can be deduced from its mass-spectrum comparing the abundances for ions $[M-15]^+$, $[M-50]^+$ and $[M-70]^+$. A methoxyl *ortho* to the diphenyl ether bridge give rise to a large and often dominating fragment $[M-50]^+$ ($[M-CH_3Cl]^+$) interpreted as a dioxin type fragment, whereas in the *para*-position the loss of a methyl radical from the molecular ion results in a stable oxonium ion, $[M-15]^+$. In contrast, a methoxyl in the *meta*-position does not favour formation of these ions, instead the dominating way of fragmentation is often loss of chlorine to $[M-70]^+$.

The methyl derivatives **3-5**, although all containing one TCG-derived methoxy group *ortho* to the diphenyl ether bridge, nevertheless give no dominating fragment $[M-50]^+$. The observed fragmentations (Table 1) are instead compatible with a methoxy group *para* (**3,5**) or *meta* (**4**) to the ether bridge. These results point strongly against carbon-oxygen coupling in position 3 or 6 of **1** but

favour coupling - with loss of chloride - in position 4 or 5. For sterical reasons, coupling in position 4 would appear less probable. The proposed structure **3** was eventually fully confirmed by X-ray crystallography *(14)*.

The formation from 4,5,6-TCG of a single dimerised isomer **1** in high yield points to an initial formation of a 3,4,5-trichloro-*o*-quinone (3,4,5-TCQ) via oxidative demethylation of 4,5,6-TCG (scheme 2.) Nucleophilic addition of unchanged 4,5,6-TCG to the least hindered position 5 of 3,4,5-TCQ followed by loss of chloride should give **1**. The apparently very high reactivity of the postulated but so far not described 3,4,5-TCQ has bearings on Michael type additions of S- and N-type nucleophiles to nascent *o*-quinones *(15)*.



3,4,5-TCQ

Scheme 2.

Oxidation of 4,5,6-TCG along scheme 2 is postulated to proceed via two one-electron steps to an intermediate phenoxonium ion. The mechanism of the final demethylation step most probably resembles that of similar reactions, e.g. periodate mediated oxidative demethylation of guaiacol *(16)* found to proceed via aryl-oxygen fission *(16,17)*.

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4. A coupling was typically performed on 250 mg of 4,5,6-TCG dissolved in 5 L water.
5. made from equal volumes of 0.36 M potassium hexacyanoferrate(III) and 0.18 M iron(III) sulphate.
6. Added as a saturated solution to 20 times the molar amount of iron(III) hexacyanoferrate(III).
7. m.p. 183-187°C. Anal. calcd. for $C_{13}H_5O_4Cl_5$ (Mw 402.4): C,38.8; H,1.2; Cl,44.1. Found C,39.4; H,1.5; Cl,44.2. IR($CDCl_3$): 2940(broad), 2850, 1670, 1605 cm^{-1}. ^{1}H-NMR:(δ ppm) 7.12(s,1H), 5.45(s,1H), 3.88(s,3H). ^{13}C-NMR:(δ ppm) 175.7(C=O), 170.4(C=O), 167.0(C-O), 160.9(C-O), 150.0(C-O), 141.1(C-Cl), 136.6(C-Cl), 134.1(C-Cl), 132,9(C-Cl), 128.3 (C-Cl), 112.8(C-H), 104.1(C-H), 56.8(C-H_3). EIMS(70eV):m/z(%), 400(M^+,<5), 372(6), 337(11), 322(9), 211(33), 162(100). Calculations based upon fragments containing ^{35}Cl only.

8. Attempts to separate **1** from the by-product by recrystallisation were unsuccessful. Instead **1** was made to precipitate from a large volume of water. After this treatment no traces of the by-product in **1** could be detected on TLC. TLC-system: MeOH:H_2O 9:1 on reversed phase C-18 pre-coated plates (Merck, Darmstadt, FRG). R_f-values for **1**, 4,5,6-TCG and by-product are 0.29, 0.45, 0.61 respectively.
9. The crude coupling product **1** was dissolved in CH_2Cl_2 (0.6M). Ascorbic acid was added as a 15 M aqueous solution to 25 times the molar amount of **1**. After stirring for 2-3h at room temperature, the organic phase was withdrawn. The product was crystallised from CH_2Cl_2.
10. mp 172-173°C. Anal. calcd. for $C_{13}H_7O_4Cl_5$ (Mw 404.5): C,38.6; H,1.7; Cl,43.8. Found C,38.0; H,1.6; Cl,43.8. ^{1}H-NMR:(δ ppm) 8.26(s,1H), 7.58(s,1H), 7.14 (s,1H), 6.04(s,1H), 3,81(s,3H). ^{13}C-NMR:(δ ppm) 151.3(C-O), 145.4(C-O), 144.1(C-O), 139.3(C-O), 137.6(C-O), 129.5(C-Cl), 128.4(C-Cl), 122.5(C-Cl), 120.3(C-Cl), 112.2(C-H), 110.4(C-Cl), 100.1(C-H), 56.1($C-H_3$). EIMS(20eV):m/z(%), 402(M^+,16), 226(100), 211(27). Calculations based upon fragments containing ^{35}Cl only.
11. mp. 153-155°C. Anal. calcd. for $C_{15}H_{11}O_4Cl_5$ (Mw 432.5): C,41.7; H,2.5; Cl,41.0. Found C,41.0; H,2.7; Cl,41.4. ^{1}H-NMR:(δ ppm) 7.01(s,1H), 5.94(s,1H), 3.77(s,3H), 3.74(s,3H), 3.62(s,3H). EIMS (cf Table 1).
12. GC analysis was performed on a DB-5 30 m x 0.25 mm ID, 0.025 mm film thickness with EC detector. Temperature progr. 80°C/2min-5°C/min-280°C/30min.
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14. We thank Dr. Lars Eriksson, Stockholm University for performing the X-ray analysis, to be published in an other context.
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