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Synthetic mimics of tyrosinase: catechols from *ortho*-, *meta*- and *para*-substituted phenols and copper(I) complexes

Francesco Chioccara [b], Germana Chiodini [a], Francesca Farina [a], Marco Orlandi [a], Bruno Rindone [a,*], Roberto Sebastiano [c]

[a] *Dipartimento di Scienze dell'Ambiente e del Territorio, Università di Milano, Via Emanueli, 15, I-20126 Milano, Italy*
[b] *Dipartimento di Chimica Organica e Biologica, Università di Napoli, Via Mezzocannone 16, I-80134 Napoli, Italy*
[c] *Dipartimento di Chimica del Politecnico, Via Mancinelli, 7, I-20133 Milano, Italy*

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Abstract

Catechols are obtained by reacting phenols bearing electron-withdrawing substituents at C-2, C-3 and C-4 and two copper(I) complexes, followed by dioxygen oxidation. A preference for the 3,4-catechol over the 2,3-catechol is observed with 3-substituted phenols. *Ortho* substituted phenols give very low yields in catechol. A binuclear μ-η^2:η^2-peroxocopper(II) phenolato complex is suggested to be the intermediate. Force field calculations permit explanation of the observed reactivity and the regiochemistry noted with *meta*-substituted compounds.

Keywords: Catechols; Copper complexes; Force field calculations; Tyrosinase

Much work has been devoted to the understanding of the conversion of phenols to *o*-quinones by the binuclear copper enzyme tyrosinase, the enzyme involved in the transformation of tyrosine into dopa along the biosynthesis of melanin [1].

Mimicking the *ortho* phenolase activity of tyrosinase has proved to be very difficult, since the oxidation of phenols often leads to phenol coupling products, owing to the intermediate formation of the persistent phenoxy radical. A mixture of *ortho*- and *para*-hydroxylated products is obtained when polymerization is avoided. Furthermore, a major problem is the high sensitivity of the resulting diphenol to oxidation conditions. This results in the oxidation to quinones with subsequent polymerization.

Regioselection is observed in metal-centered hydroxylations of phenols: the *para* regiochemistry is observed in some cobalt-centered reactions [2], and the *ortho* regiochemistry is obtained in copper-centered systems, which have been studied as potential mimics of tyrosinase activity [1].

In a previous paper [3] we reported a stoichiometric copper(I)-centered method which transforms phenols into catechols. The reactant was a very easily available [4] mononuclear Cu(I) complex, PhenCu(I)PPh_3BH_4 (1). This is one of the few available examples of selective *ortho*-hydroxylation of a phenol by a copper reactant. In fact, other copper reactants such as Cu_2Cl_2/Cu [5] or Cu(I)/amine [6] give the *ortho*-hydroxylation of phenols, but also the *para*-hydroxylation reaction and the subsequent phenol oxidative

* Corresponding author.

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Table 1
Reaction conditions and yields in the *ortho*-hydroxylation of phenols with the copper(I) borohydrido complex (**1**)

R–C_6H_5–OH	Solvent	[Cu]/[S] ratio	Cu(I) phenoxo complex formation		Oxidation conditions		Catechol yields %	
R=			*t* (h)	*T* (°C)	*t* (h)	*T* (°C)	2,3-	3,4-
H (**3**)	THF	1:5	24	40	24	25		(27):100
4-COOMe (**6**)	THF	1:8	1	25	20	25		(28):96
4-COOMe (**6**)	THF	1:2	24	40	18	25		(28):76
4-COOMe (**6**)	THF	1:8	1	25	18	25		(28):90
4-COOMe (**6**)	AN	1:8	3	25	18	25		(28):–
3-COOMe (**7**)	THF	1:8	6	25	16	25	(35):11	(28):34
3-COOMe (**7**)	THF	1:2	24	40	18	25	(35):24	(28):49
2-COOMe (**8**)	THF	1:2	24	40	18	25	(35):2	
4-CH=CH–COOMe (**9**)	THF	1:8	1	25	18	25		(29):90
4-CH=CH–COOMe (**9**)	THF	1:2	24	40	18	25		(29):75
3-CH=CH–COOMe (**10**)	THF	1:2	24	40	18	25	(36):10	(29):20
2-CH=CH–COOMe (**11**)	THF	1:2	24	40	18	25	(36):6	
4-Cl (**12**)	THF	1:2	24	40	18	25		(30):24
3-Cl (**13**)	THF	1:2	24	40	18	25	(37):2	(30):5
2-Cl (**14**)	THF	1:2	24	40	18	25	(37):4	
4-CHO (**15**)	THF	1:2	24	40	18	30		(31):12
3-CHO (**16**)	THF	1:2	24	40	18	30	(38):–	(31):14
2-CHO (**17**)	THF	1:2	24	40	18	30	(38):–	
4-NO_2 (**18**)	THF	1:2	24	40	18	30		(32):tr
4-NO_2 (**18**)	THF	1:8	1	25	18	40		(32):–
4-NO_2 (**18**)	AN	1:8	3	25	1	40		(32):33
3-NO_2 (**19**)	THF	1:2	24	40	18	30	(39):–	(32):tr
2-NO_2 (**20**)	THF	1:2	24	40	18	30	(39):tr	
4-CH_2–COOMe (**21**)	THF	1:2	24	40	3	30		(33):5
3-CH_2–COOMe (**22**)	THF	1:2	24	40	3	30		(33):3
2-CH_2–COOMe (**23**)	THF	1:2	24	40	3	30	(40):16	
2-CH_3 (**24**)	THF	1:8	24	45	12	25		(41):28
4-$C(CH_3)_3$ (**25**)	THF	1:8	24	40	12	25		(34):25
2,6-di-$C(CH_3)_3$ (**26**)	THF	1:8	3	25	36	25		(42):65

coupling occur [7] as the result of the intermediate formation of Cu(II)/dioxygen reactants [8].

A key feature of the PhenCu(I)PPh_3BH_4-mediated hydroxylation reaction is the intermediate formation of a copper(II) catecholate complex which releases the catechol only after aqueous HCl treatment. Hence, no free catechol is present in the solution containing dioxygen and eventually copper(II). This avoids further oxidation of any free catechol to a quinone and subsequent polymerization, as observed in blank experiments performed reacting the catechols with copper(II) ions and dioxygen.

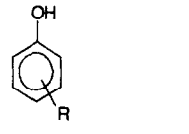
The *ortho*-hydroxylation of phenols is also obtained using Cu(I) complexes with binucleating ligands such as *meta*-xylyldiamine derivatives [9] or a Schiff base [10]. They in fact catalyze the oxidation of 2,4-di-t-butylphenol to the corresponding *ortho*-quinone.

These systems have several advantages over other catechol-forming reactions: the acid-catalysed rearrangement of *O*-aryl-*N*-benzoylhydroxylamines [11], the hydrogen peroxide oxidation of *ortho*-hydroxyacetophenone [12], the benzeneseleninic anhydride oxidation of phenols [13], which require the synthesis of the appropriate precursor.

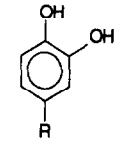
Several *ortho*-, *meta*- and *para*-substituted phenols were reacted with the copper(I) tetrahydroborate complex (1) either in tetrahydrofuran (THF) or in acetone (AN) using a 8:1 or 2:1 phenol:substrate ratio. The resulting suspension was then treated with dioxygen. The isolation of

the reaction products was performed by silica gel chromatography. The results are shown in Table 1. The yields were calculated according to the following stoichiometric equation and are referred to Cu(I) added:

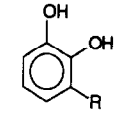
$$\text{phenol} + 2\text{Cu(I)} + \tfrac{1}{2}O_2 \rightarrow \text{catechol} + 2\text{Cu(II)}$$



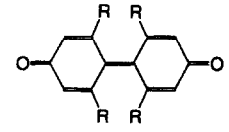
(3): R = H
(6): R = 4-COOMe
(7): R = 3-COOMe
(8) : R = 2-COOMe
(9) : R = 4-CH=CH-COOMe
(10) : R = 3-CH=CH-COOMe
(11) : R = 2-CH=CH-COOMe
(12) : R = 4-Cl
(13) : R = 3-Cl
(14) : R = 2-Cl
(15) : R = 4-CHO
(16) : R = 3-CHO
(17) : R = 2-CHO
(18) : R = 4-NO_2
(19) : R = 3-NO_2
(20) : R = 2-NO_2
(21) : R = 4-CH_2-COOMe
(22) : R = 3-CH_2-COOMe
(23) : R = 2-CH_2-COOMe
(24) : R = 2-Me
(25) : R = 4-CMe_3
(26) : R = 2,6-di-CMe_3



(27) : R = H
(28) : R = 4-COOMe
(29) : R = 4-CH=CH-COOMe
(30) : R = 4-Cl
(31) : R = 4-CHO
(32) : R = 4-NO_2
(33) : R = 4-CH_2-COOMe
(34) : R = 4-CMe_3



(35) : R = 3-COOMe
(36) : R = 3-CH=CH-COOMe
(37) : R = 3-Cl
(38) : R = 3-CHO
(39) : R = 3-NO_2
(40) : R = 3-CH_2-COOMe
(41) : R = 3-Me



(42) : R = CMe_3

Phenol (**3**) itself was converted into the catechol (**27**) in THF in quantitative yield. Some information about the oxygenation step was obtained from this reaction. In fact, the oxygenation of the preformed complex (**4**: R = H) is irreversible and permitted us to isolate the copper(II)phenolato catecholato complex (**5**: R = H) which gives the catechol upon acidic treatment [4] (Scheme 1).

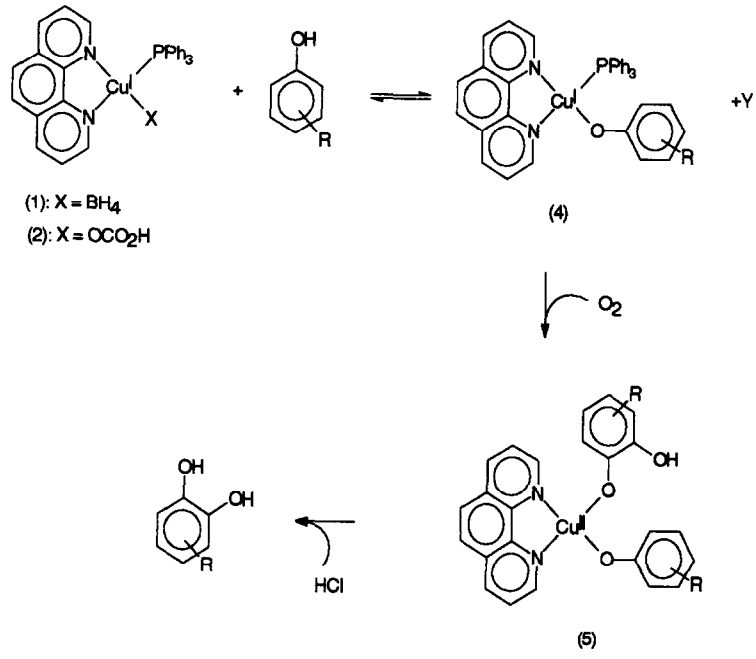
The catechol (**28**) was always obtained in high yield from methyl-4-hydroxybenzoate (**6**) using THF as the solvent. The starting material was quantitatively isolated when AN was the solvent. Hence, THF was a suitable solvent for this substrate and was used for the hydroxylation of methyl 3-hydroxybenzoate (**7**). This gave two isomeric catechols upon hydroxylation both in phenol:Cu complex ratios 8:1 and 2:1. The 3,4-catechol (**28**) was favoured over the 2,3-catechol (**35**) by a factor of 3 in the former case, and by a factor of 2 in the latter conditions. Methyl 2-hydroxybenzoate (**8**) was much less reactive, and a very small amount of the corresponding catechol (**35**) was formed.

A very similar situation occurred with *E*-methyl-4-hydroxy (**9**), 3-hydroxy (**10**) and 2-hydroxy cinnamate (**11**). In THF the *para*- and the *meta*-substituted compound gave good hydroxylation yields, the *ortho*-substituted compound was much less reactive. Again, the regiochemistry of the hydroxylation of the *meta*-isomer (**10**) favoured the 3,4-isomer (**29**) over the 2,3-isomer (**36**) by a factor of 2.

Chlorophenols (**12–14**) gave catechols (**30**) and (**37**) in very poor yields. In the case of hydroxybenzaldehydes (**15–17**), the concurrent reduction of the aldehydic carbonyl gave mixtures of benzyl alcohols. The isomeric nitrophenols (**18–20**) were nearly unreactive using THF as the solvent. On the contrary, when 4-nitrophenol was hydroxylated in AN, a moderate amount of the catechol (**32**) was isolated.

A second group of phenols submitted to the hydroxylation reaction in THF had electron-releasing groups attached to the aromatic nucleus. They were the methyl hydroxyphenylacetates (**21–23**). Here, the catechols (**33**) and (**40**) were isolated in minute amounts since they were further oxidized during the oxygenation step. In fact, methyl 3,4-dihydroxy benzoate (**28**) was detected after diazomethane methylation of the reaction mixture. This compound derived from the oxidation of the benzylic methylene carbon.

Further substrates of this type were 2-methylphenol (**24**), and 4-t-butylphenol (**25**), which



Scheme 1.

were hydroxylated in THF to the catechols (**41**) and (**34**).

2,6-Di-t-butylphenol (**26**) was catalytically converted into the dimeric quinone (**42**) when submitted to the same reaction conditions.

A different procedure was assayed by reacting three phenols with the copper(I)carbonato complex (**2**) [4]. Table 2 shows that a quantitative yield in catechol (**27**) from phenol (**3**) and in 3,4-dihydroxynitrobenzene (**32**) from 4-nitrophenol (**18**) were obtained only using AN as the solvent. Methyl 4-hydroxy benzoate (**6**) was almost unreactive both in THF and in AN.

A key step in this hydroxylation reaction seems to be the equilibrium complexation of the phenol to the copper(I) reactant. In fact, the reaction of excess phenol (Scheme 1) with the copper(I) tetrahydroborate complex (**1**) ($Y = BH_3 + H_2$) or the copper(I) carbonato complex (**2**) ($Y = CO_2 + H_2O$) in tetrahydrofuran allows the isolation of the Cu(I) phenolate complex (**4**: R = H) [4], characterized by an UV absorption band at 320 nm.

The nature of the copper(I) reactant leading to the equilibrium formation of the Cu(I) phenolate complex (**4**) seems to be crucial in this reaction. In fact, methyl 4-hydroxybenzoate (**6**) is hydroxylated by the Cu(I) tetrahydroborate complex (**1**), but not by the Cu(I)carbonato complex (**2**). The formation of water from the latter reactant

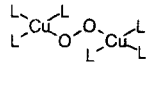
Table 2
Reaction conditions and yields in the *ortho*-hydroxylation of phenols with the copper(I) carbonato complex (**2**)

R–C_6H_5–OH	Solvent	[Cu]/[S] ratio	Cu(I) phenoxo complex formation		Oxidation conditions		Catechol yields %
R =			*t* (h)	*T* (°C)	*t* (h)	*T* (°C)	3,4-
H (**3**)	AN	1:8	12	25	1	25	(6):100
H (**3**)	THF	1:8	12	25	1	25	(6):tr
4-COOMe (**6**)	THF	1:8	2	50	12	25	(28):tr
4-COOMe (**6**)	AN	1:8	2	50	12	25	(28):–
4-NO_2 (**18**)	AN	1:2.4	3	25	2	50	(32):100

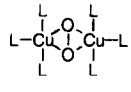
and the consequent hydrolysis of the copper (I) phenolate complex is probably responsible for this behaviour. Also the solvent is important, since 4-nitrophenol (**18**) is hydroxylated by both Cu(I) complexes in AN, but not in THF. Hence, the presence of water, the solvent, the solubility of the reactants and the temperature are important in the formation of the copper(I) complex. In fact, it is formed in an equilibrium reaction.

In addition, the nature of the substrate influences the formation of the copper(I) phenolato complex (**44**). The reaction seems to be favoured by the acidity of the phenol. In fact, several hours reaction and mild heating are necessary for the formation of complex (**44**) from the less acidic phenols (e.g. those bearing electron-releasing groups).

It has however recently pointed out that oxytyrosinase and oxyhemocyanine have a Cu–Cu distance of 3.63 [14] and 3.58–3.66 Å [15], respectively, which is far enough from the corresponding values observed for synthetic *trans* μ-1,2-peroxo binuclear copper(II) complexes (**43**) (4.359 Å) [16]. A distorted square pyramidal μ-η^2:η^2 structure (**44**) having a Cu–Cu distance of 3.55 Å and O–O distance of 1.40 Å has recently been observed in a synthetic complex. These data are consistent with the parameters of the two oxyenzymes [17].



(43)



(44)

The former is suggested to be a nucleophilic oxygenation reagent, whereas the latter is suggested to be an electrophilic oxygenation reagent [18].

A study of electronic effects reveals that electron-rich ligands are hydroxylated faster. Moreover, the NIH shift is observed [19]. These data suggested that a binuclear μ-η^2:η^2-peroxocopper(II) is the intermediate in these reactions.

The results obtained in the present work suggest that the mode of oxygenation of the mononuclear copper(I) complex (**44**) is similar to the oxygenation of some mononuclear copper(I) complexes which form binuclear *trans* copper(II) 1,2- peroxo [20] and μ-η^2:η^2-peroxo [21] complexes. The subsequent oxygenation of the phenolate ligand is faster when electron-releasing groups are attached to the phenyl ring than when electron-withdrawing substituents are present. Hence, it is electrophilic in nature, suggesting that the reactant has a binuclear μ-η^2:η^2-peroxocopper(II) phenolato complex structure.

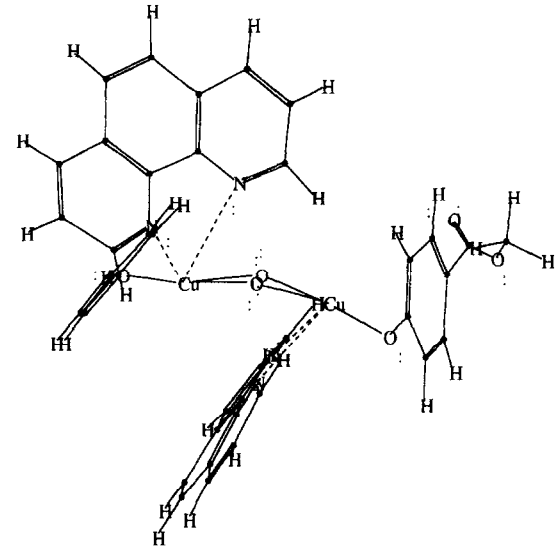


Fig. 1. Bisphenoxobisphenanthrolinocopper(II) μ-η^2:η^2-peroxo complex after MMX minimization.

Reaction intermediates of this type have not yet been isolated. Hence, the application of force field calculations [22] was a possibility to obtain structural information to be compared with those of the very few compound known. This procedure had given excellent results when used for rigid ruthenium(0) clusters [23]. The conformational analysis of these models could also be useful to explain the low conversion observed with *ortho*-substituted phenols, and the slight preference of the formation of the 3,4-catechol over the 2,3-catechol in the hydroxylation of *meta*-substituted phenols.

Calculations were performed using the Cu–Cu distances (3.60 Å) and O–O (1.40 Å) found in the literature [20] and selecting structures having coplanarity of each copper atom and its phenanthroline ligand. Fig. 1 shows the bisphenoxobis-

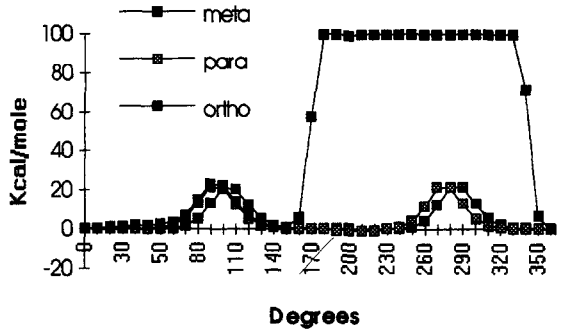
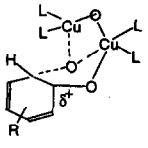


Fig. 2. The energy profile for the rotation of the carbon-oxygen bond in the isomeric *ortho*-, *meta*- and *para*-carbomethoxybisphenoxobisphenanthrolinocopper(II) μ-η^2:η^2-peroxo complex.

phenanthrolinocopper(II) μ-η^2:η^2-peroxo complex after MMX minimization. These structures were chosen because could be precursors of the phenolato catecholato copper(II) complex (**45**) isolated earlier.

The reactivity profile observed: *para* > *meta* > *ortho*, was studied analyzing the energy profile upon rotation of the phenyl group of one of the phenoxo ligands around the carbon–oxygen bond. Fig. 2 shows the results obtained for the isomeric *ortho*-, *meta*- and *para*-carbomethoxybisphenoxobisphenanthrolinocopper(II) μ-η^2:η^2-peroxo complex. These calculations show that the free rotation is hindered by two maxima at 20.57 and 20.83 kcal/mol for the *para* isomer, at 20.81 and 21.41 kcal/mol for the *meta* isomer, and a very high energy barrier occurs with the *ortho* isomer. The same situation occurred with the cinnamylphenoxo and the chlorophenoxo isomers.

If one assumes a cyclic half chair intermediate for the oxygen transfer reaction:



the population of the conformation having a short distance between the *ortho* carbon of the phenoxy group and one of the two peroxidic oxygens could explain the reactivity profile noticed for *para*-, *meta*- and *ortho*-isomers. These distances were calculated for the *meta*-carbomethoxybisphenoxobisphenanthrolinocopper(II) μ-η^2:η^2-peroxo complex and are shown in Fig. 3. These calculations show that on rotating the phenyl group, one of the carbon atoms *ortho* to the phenoxo oxygen is slightly more than 3 Å away from one of the peroxidic oxygens. Hence, the freer is the rotation around this bond, the higher will be the population of the conformer having a short distance between the *ortho* carbon and the peroxidic oxygen to be transferred. In the case of the *ortho* isomer, the energy barrier among different conformers allows that only one fraction of the conformers of the *ortho*-substituted compound can transfer oxygen. This explain the poor yields in the catechol noticed with *ortho*-substituted compounds.

Also the regiochemistry in the hydroxylation of the *meta* substituted phenol is probably due to kinetic control in the transfer of the oxygen atom to the *ortho* carbon in the bisphenoxo μ-η^2:η^2-peroxo complex. In fact the conformation obtained rotating the phenyl–oxygen bond at 90° has the lowest distance between one peroxidic hydrogen and the *ortho* carbon leading to the 2,3-catechol, but is an energetically unstable (12.71 kcal/mol), whereas the conformation at 240°, which leads to the 3,4-catechol, has a slightly greater distance, but is much more stable (0.05 kcal/mol).

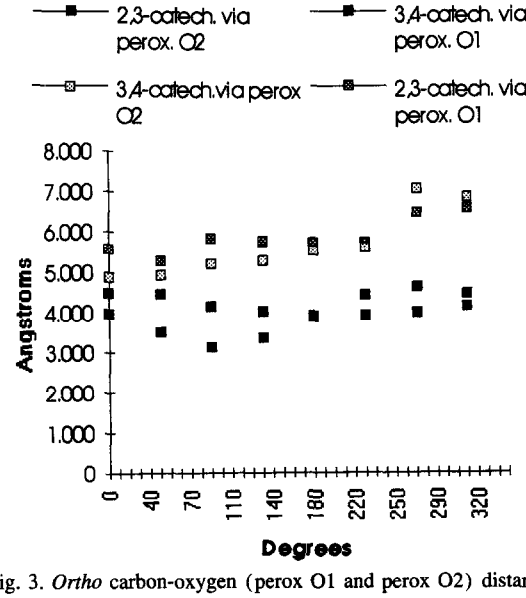


Fig. 3. *Ortho* carbon-oxygen (perox O1 and perox O2) distances calculated for the *meta*-carbomethoxybisphenoxobisphenanthrolinocopper(II) μ-η^2:η^2-peroxo complex.

1. Experimental

1.1. General procedure

The appropriate phenol (1.6 mmol) and the required amount of the copper(I) complex (**1**) were dissolved in tetrahydrofuran or acetone (10 ml) previously deoxygenated with a nitrogen stream and the mixture was stirred under nitrogen for the required time. Dioxygen was then introduced into the reaction vessel. Tables 1 and 2 report the temperature and the time for these two steps.

At the end of the oxygenation, the reaction mixture was diluted with ethyl acetate (20 ml) and washed with 10 ml of 2 M HCl. The aqueous layer was extracted twice with ethyl acetate (10 ml portions) and the combined organic extracts were dried over sodium sulphate. Removal of the solvent under reduced pressure afforded a residue which was fractionated over silica gel 0.05–0.2 mesh ($R=100$), eluting with chloroform and chloroform methanol 1:1 mixtures. The crude reaction mixture was also analyzed by gas chromatography and reverse phase high performance liquid chromatography, a comparison being made with authentic samples of the expected catechols. A working curve using standard compounds allowed to obtain reaction yields.

Acknowledgements

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