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Review on "*para*-Alkoxyphenols": an important group of antimelanoma compounds

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ABSTRACT

Melanoma is the most lethal cancer of the skin, and the number of incidence of melanoma worldwide has doubled in the past twenty years. Once malignant melanoma has progressed to the metastatic stage, it becomes refractory to treatment with currently available therapies.p-alkoxyphenols form an important group of antimelanoma compounds.

Keywords: para-Alkoxyphenol, Antimelanoma compounds, RNR, Cytotoxicity and Radical scavenger

I. INTRODUCTION

It has been known that *p*-alkoxyphenols form an important group of antimelanoma compounds [1]. Two important approaches in developing *p*-alkoxyphenols as anti-melanoma agents are based on their (i) ribonucleotide reductase (RNR) inhibition activity[2] and (ii) tyrosinase dependent cytotoxicity[3]. In the first approach, the reduction of ribonucleotides, which provide the building blocks for DNA replication and repair in all living cells, is inhibited by quenching of a tyrosyl free radical through interaction of *p*-alkoxyphenol with RNR protein R 2.[2] In the second approach, *p*-alkoxyphenols and related phenol-based prodrugs are bioactivated to catechols and then to quinones in melanoma cells as a result of their oxidation by tyrosinase. The quinones so generated exert their cytotoxicity by causing intracellular glutathione depletion of melanoma cells[3].

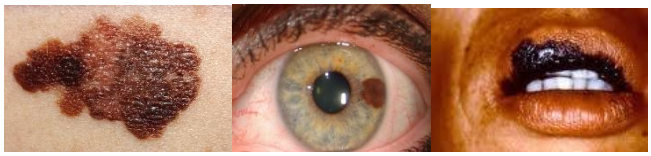

Fig 1: Different types of Skin Cancer

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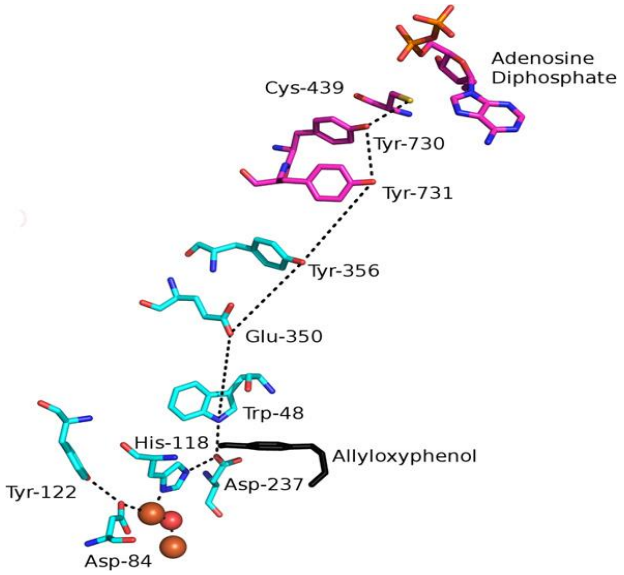


Fig 2: Ribonucleotide Reductase (RNR) Inhibition

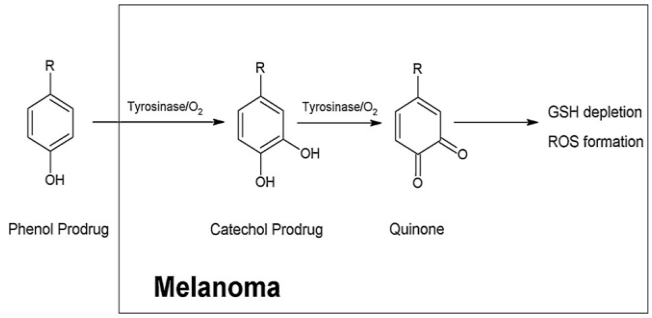


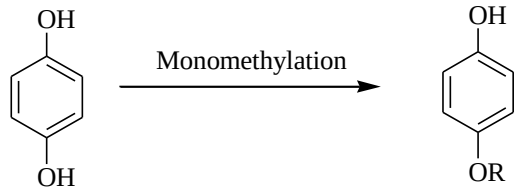
Fig 3: Tyrosine Dependent Cytotoxicity

The RNR inhibition activity of *p*-alkoxyphenols mentioned above not only develops their anti-melanoma property but also makes them effective against bacteria and viruses, *e.g.*, it is known that the deoxyribonucleic acid pools of HIV or HSV-infected cells are exhausted by their action.[2,4] All these biological activities along with the general radical scavenging activities of *p*-alkoxyphenols [5] make their laboratory synthesis important.

II. METHODS

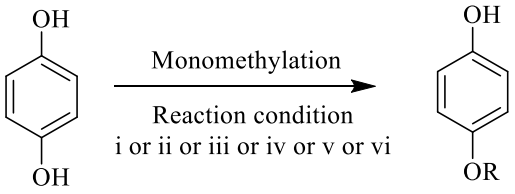
The general routes for synthesis of *p*-alkoxyphenols are partial alkylation of quinol [6,7] by use of common alkylating agents like alkyl sulphates by Robinson et al.[6a] or alkyl halides by Zhang et al. [6b] and Newman et al. in 1974. [6c] as well as by use of alcohols in presence of different catalytic systems. [7] Baeyer-Villiger reaction of *p*-alkoxybenzaldehydes or *p*-alkoxyketones [8] or acid catalyzed hydrogen peroxide oxidation of *p*-alkoxybenzaldehydes, [9] cyclization of suitable Fischer carbenes,[10] and controlled dealkylation of *p*-dialkoxybenzenes by substoichiometric amount of AlI_3[11a] or BBr_3.[11b] Moreover, a two-step conversion of *p*-benzoquinone to *p*-alkoxyphenols by reaction of the former with $P(OR)_3$ followed by alkaline hydrolysis of the intermediate is known.[12]

2.1 Monomethylation using common alkylating agents (Scheme-1):



i) R_2SO_4, NaOH, 12 °C, 5 min—[6a]
HCl, 8 °C, 1 h
ii) (a) α-bromoisobutyrate, NaH---[6c]
DMSO, 80 °C, 2 h
(b) tert-butyl bromoacetate
NaOH, 1:1 dioxane-water, rt., 1h, N_2-atm.
iii) R_2SO_4, RX, KOH, rt., 9 days—[6d]
iv) RX, ROH, reflux, 3 h----[6e]
v) ROR, silica-alumina catalyst— [7a]

2.2 Monomethylation using alcohols as alkylating agents(Scheme-2):



i) ROH, $Al(OH)_3$, H_3BO_3 & H_3PO_4 --[Ref.8b]
ii) ROH, H_2SO_4----------[Ref.8d]
iii) ROH, $CuCl_2/FeCl_3/Fe_2SO_4.7H_2O$,$CuCl+O_2$ --------[7e]
iv) ROH, $H_2O_2/HClO_4$----[Ref.8g]
v) ROH, Phosphomolybdic acid

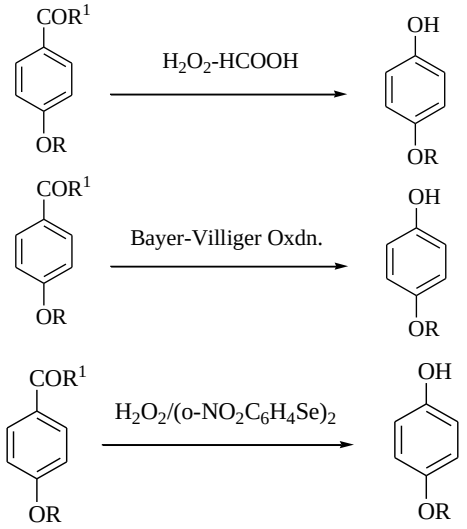
—[7i]

Phosphotungstic acid,

silicotungstic acid

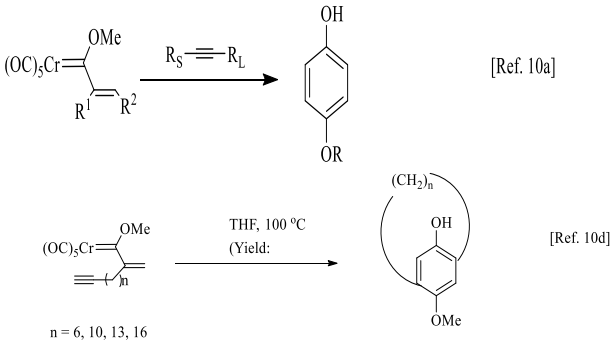
vi) ROH, transition metal(e.g; Cu, Cr, Zn, Co, Ni, Mn) --[7k]

2.3 Baeyer-Villiger reaction of *p*-alkoxybenzal dehydes or *p*-alkoxyketones and related reac tion (Scheme-3, Scheme-4, Scheme-5):

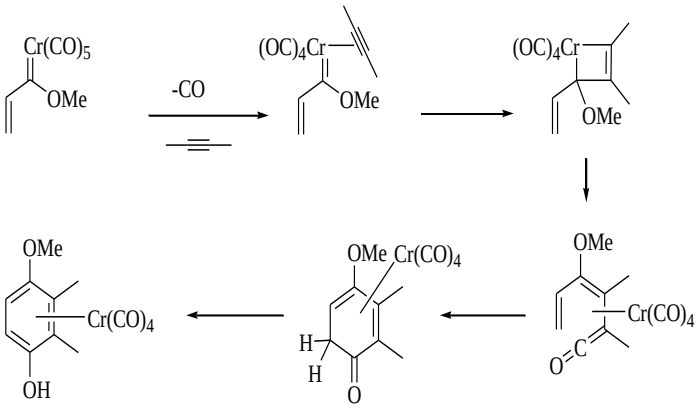


R^1 = H, alkyl group

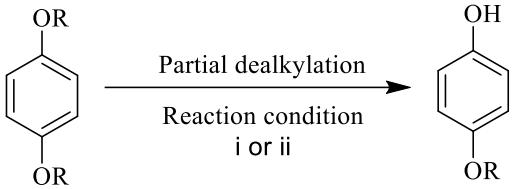
2.4 Cyclization of suitable Fischer carbenes(Scheme-6):



***Mechanistic aspects (as proposed by* Dötz*)* (Scheme-7):** [9a]:



Controlled dealkylation of *p*-dialkoxybenzenes (Scheme-8):

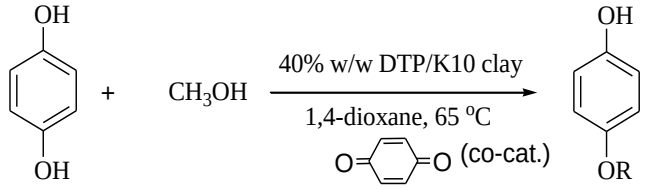


i) AlI_3 / CH_3CN or CS_2/3-5 h, reflux-----[Ref.12a]

ii) BBr_3 / CH_2Cl_2, rt.,1.5-24 h----------[Ref.12b]

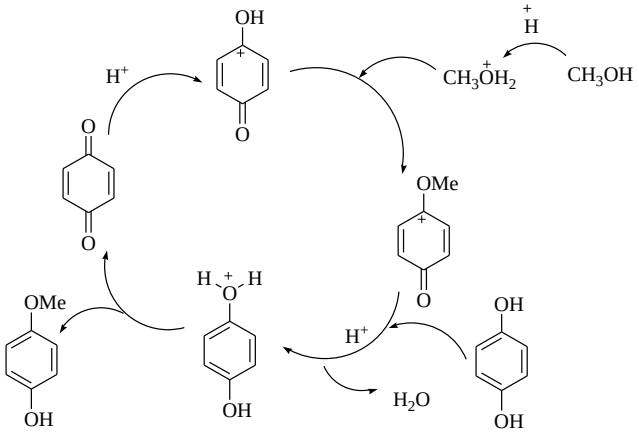
The routes involving alkylation of quinol by use of alcohols have been reported in a number of patents [7]. However, in none of them the mechanistic aspects for the conversion has been discussed. Two mechanistic possibilities for the conversion are i) direct partial alkylation of quinol, and ii) an oxidation of quinol to *p*-benzoquinone followed by conversion of the latter to the *p*-alkoxyphenols. In the second possibility the last step would require a reduction process, and here quinol or alcohol, which is the reducing agent that is an important aspect requiring clarification. In a recent paper Yadav *et al.*[13] have reported the conversion of quinol to *p*-methoxyphenol (Scheme-9) by the reaction of the former with methanol in presence of 40% dodecatungstophosphoric acid (DTP)/montmorillonite clay (K10) as catalyst and benzoquinone as cocatalyst. Regarding the mechanistic aspect of the conversion,

they suggested that protonated quinone is first methylated and then the resulting species is reduced with protonated quinol and a chain process is set up, which continues up to the end.

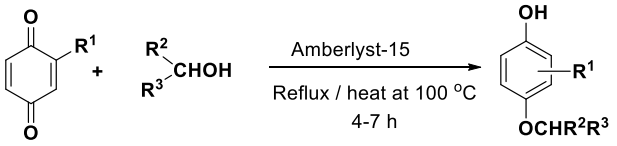


Dodecatungstophosphoric acid (DTP)/montmorillonite clay (K10)

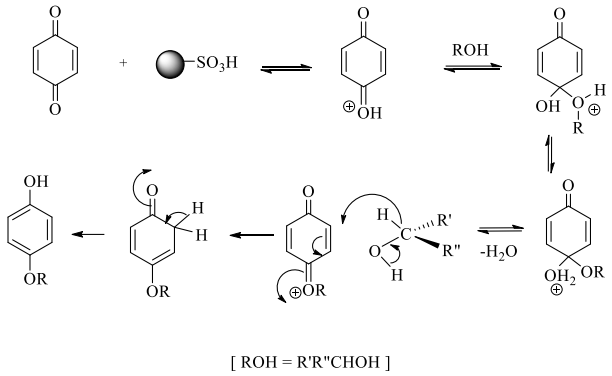
Mechanism for Etherification of Hydroquinone with Methanol (Scheme-10):



Mallik et al.[14] also reported the synthesis of *para*-alkoxyphenol from *para*-benzoquinone by using of amberlyst-15(Scheme-11).



Plausible Mechanism for Formation of *para*-alkoxyphenol (Scheme-12):



[ROH = R'R"CHOH]

III.CONCLUSION

From the investigation, it is concluded that, *para*-alkoxyphenols which is known as anantimelanoma compounds has been synthesized using different methods.

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