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ON THE REGIOSELECTIVITY OF THE FREMY'S SALT OXIDATION OF PHENOLS

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Abstract - A detailed study of the regioselectivity of the Fremy's salt oxidation of phenols, including a series of MNDO calculations of the intermediate phenoxy radicals, has been carried out. The analysis of these results has led us to establish a new rule for the para vs. ortho regioselectivity, namely: "C-4 unsubstituted phenols, as well as phenols substituted at C-4 with easy-to-displace groups, undergo oxidation (or oxidative degradation) by the action of Fremy's salt, thus eventually providing the corresponding p-quinones". A similar rule for the ortho vs. ortho' regioselectivity could not be so precisely formulated since now steric effects play a significant major role.

Mainly through the extensive efforts of Teuber and coworkers, the mechanism of the oxidation of phenols by Fremy's salt (F.S.)[1] is now viewed as a three step process, the first of which involves the formation of a phenoxy radical. This is then followed by coupling with a second F.S. unit at the para (or ortho) position, and, ultimately, by elimination of $HN(SO_3K)_2$ with concomitant formation of a quinone[2].

Furthermore, it is generally assumed that the F.S. oxidation of phenols having free para positions gives rise to p-quinones, whereas phenols with only free ortho positions yield o-quinones[3].

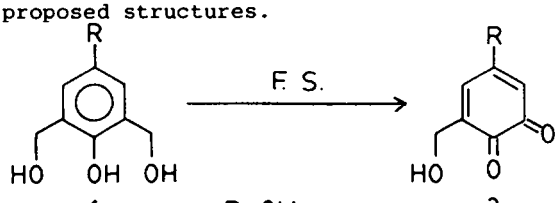
In striking contrast with the widely accepted rule above, many p-substituted phenols such as benzylalcohols[4], benzylamines[5], as well as some benzoic acids[6], benzamides and benzaldehydes[6] were proved to be highly promising p-quinone synthons In other words, they were shown to undergo a novel oxidative degradation by the action of Fremy's salt, thus yielding only the corresponding p-quinones instead of the expected o-quinones[3].

These observations together with some other unexpected results reported in the literature[7], clearly demanded a closer look into the mechanism of the so-called Teuber reaction. More specifically, a precise definition of the factors which control regioselectivity appeared necessary.

Therefore we planned our work to reach two main objectives. Firstly we wanted to fully explore the scope of the oxidative degradation approach (ODA) for the rational synthesis of o-quinones[4] and, secondly, we projected to investigate the responsible factors for the regioselectivity of the Teuber reaction and its oxidative degradation counterpart.

In particular, our attention was first focussed on examining the outcome of the F.S. oxidation of a series of symmetrically and unsymmetrically substituted phenols. The second part on the plan included performing MO calculations of significant phenoxy radicals. These, we reckoned, would provide us with the useful SOMO coefficients which, to a first approximation, could be directly related with the problem of regioselectivity[8]. Obviously we were assuming that the first step of the F.S. oxidation of phenols was rate determining[9] and, therefore, that the second, or ,rather, the second and third steps were those responsible for the overall regioselectivity observed.

Thereafter, in the first place, the reaction of several 4-substituted-2,6-bishydroxymethyl phenols 1 with F.S. was studied. As expected, these compounds suffered oxidative degradation to the corresponding hydroxymethyl o-quinones 2, in all cases but that of 1c which yielded recovered starting material (Scheme 1). The intrinsic labile nature of these interesting[10] o-quinones precluded the obtention of their elemental analysis. Nevertheless, their spectroscopic data are in full accordance with the proposed structures.

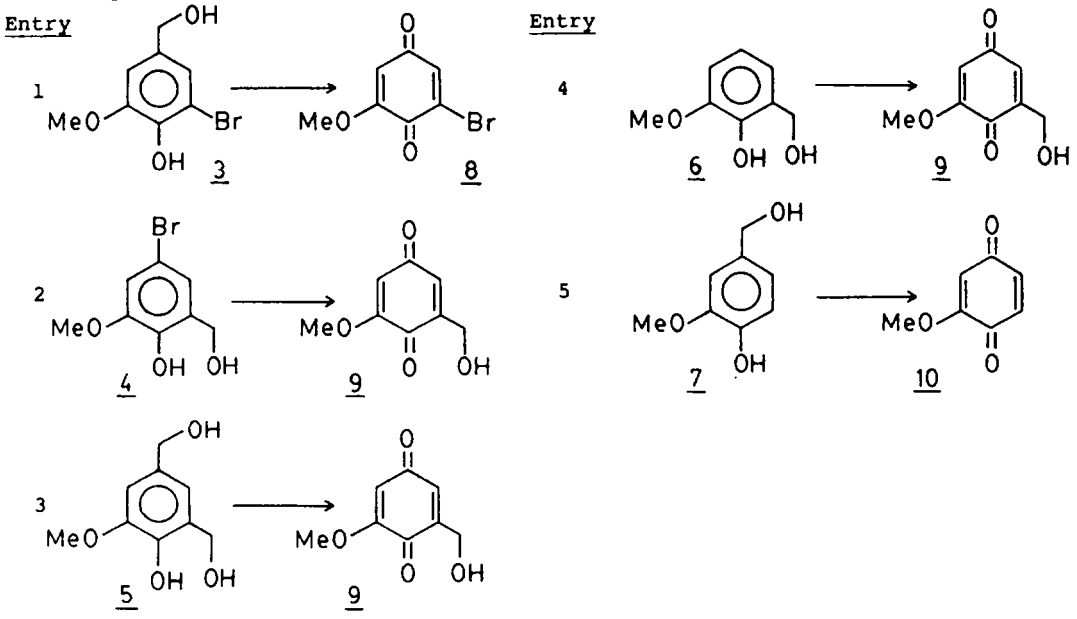


1 2

a R=OMe
b R=Me
c R=C_6H_5

Scheme 1

In the second place, we selected for treatment with F.S. a series of unsymmetrically substituted phenols, characterized by having, at least, one easy-to-displace[11] group in ortho or para. On passing, it is worth mentioning that, the orthohydroxybenzyl alcohols employed were best prepared by borohydride reduction of the corresponding aldehydes in anhydrous THF. In this manner, the formation of by-products reported to be obtained when working in polar protic solvents[12a] was a-



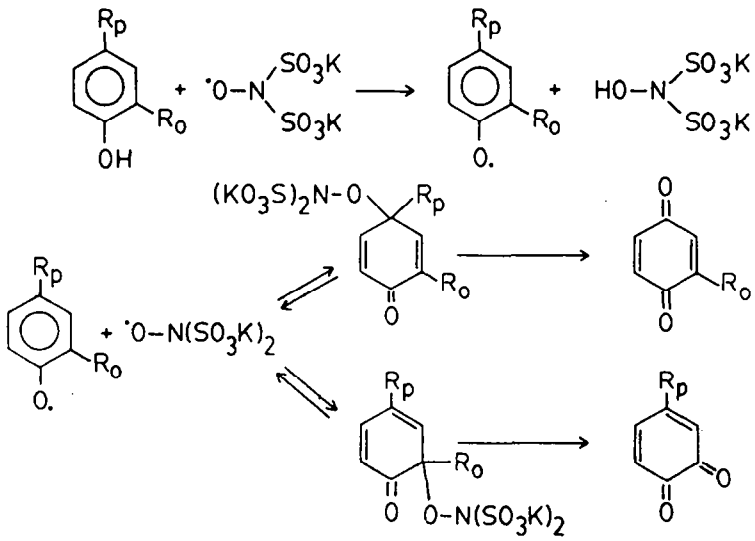
Scheme 2

voided. Moreover, in contrast with the long reaction times required when working with protic solvents[12b], the above reactions, which presumably involve phenol borate intermediates[12c], take place very rapidly.

The experimental observations carried out during the course of this and other relevant studies[13] appear illustrated in Scheme 2.

From these clear-cut observations the following rule has been derived, describing in a more precise manner the F.S. oxidation of phenols: "both C-4 unsubstituted phenols and phenols substituted at C-4 with easy-to-displace[11] groups, undergo oxidation, or oxidative degradation, by the action of F.S., thus providing the corresponding p-quinones".

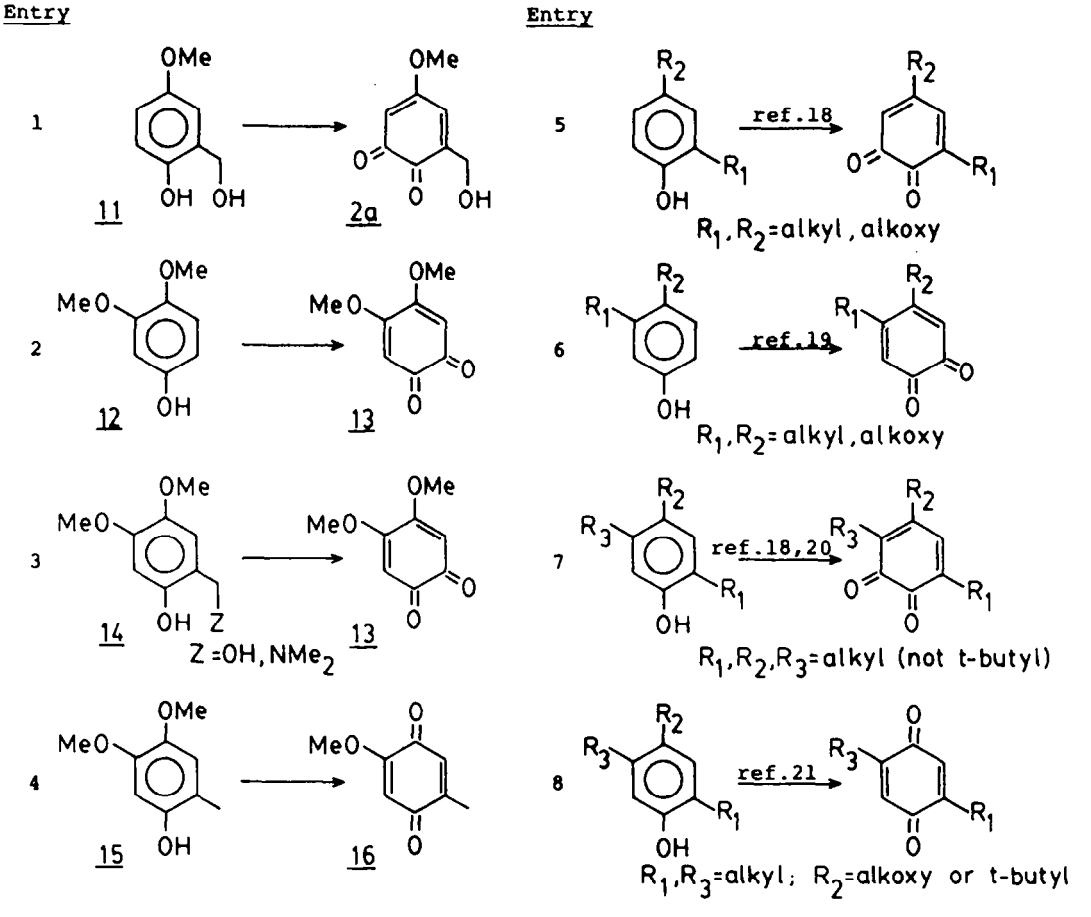
In our opinion, the driving force for this apparently general behaviour[14] lies within a reasonable assumption: phenoxy radicals must have a large SOMO coefficient at C-4. Therefore, cyclohexa-2,5-dienones result when the latter combine with F.S. during the second step of the reaction. Furthermore, for those cases where R=H (or easy-to-displace group), the so produced cyclohexadienone intermediate finds a low energy pathway for the final cleavage. In agreement with this view, the formation of o-quinones -from phenols possesing not-easy-to-displace groups at C-4- can consequently be understood as the result of the reversible[15] formation of phenoxy and F.S. radicals from the primary cyclohexa-2,5-dione intermediate. In other words, as depicted in Scheme 3, cyclohexa-2,5-dienones may isomerize to cyclohexa-2,4-dienones in a stepwise fashion[16] and, therefore, give rise to an o-quinone system, provided there is a low energy pathway for cleavage.



Scheme 3

On the other hand, as judged from the results shown in Scheme 4 (entries 1-4), the problem of ortho vs. ortho' regioselectivity appeared puzzling. Nevertheless, on examining previous reports regarding the Fremy's salt oxidation of 2,4-disubstituted, 3,4-disubstituted and 2,4,5-trisubstituted phenols (entries 5-8), it was rewarding to find that identical results to ours had already been observed by other workers[17]. Accordingly, we noticed that 2,4-disubstituted phenols provide C-6 oxidized products on treatment with F.S.[18], even when an easy-to-displace group is at C-2 (Scheme 4, entries 1,5). 3,4-Disubstituted and 2,4,5-trisubstituted phenols, on the other hand, give rise to different products as a function of the substituent at C-2. Thus, 3,4-disubstituted o-quinones result from oxidation of 3,4-disubstituted phenols[18,19] (entries 2,6), as well as from oxidation of 2,4,5-trisubstituted phenols (entry 3) when the substituent at C-2 is an easy-to-displace group (CH_2OH, CH_2NR_2). Yet, oxidation at C-6 takes place on phenols substituted at C-2 and C-4 with alkyl groups (entry 7)[18,20]. Even more surprising is the oxidative degradation

at C-4, which produces p-benzoquinones[21], suffered by phenols substituted with alkyl groups at C-2 and alkoxy groups at C-4 (entries 4,8). In the latter case an oxidative degradation, involving a not-easy-to-displace group, takes place more rapidly than simple oxidation of an unsubstituted ortho position (C-6)!.



Scheme 4

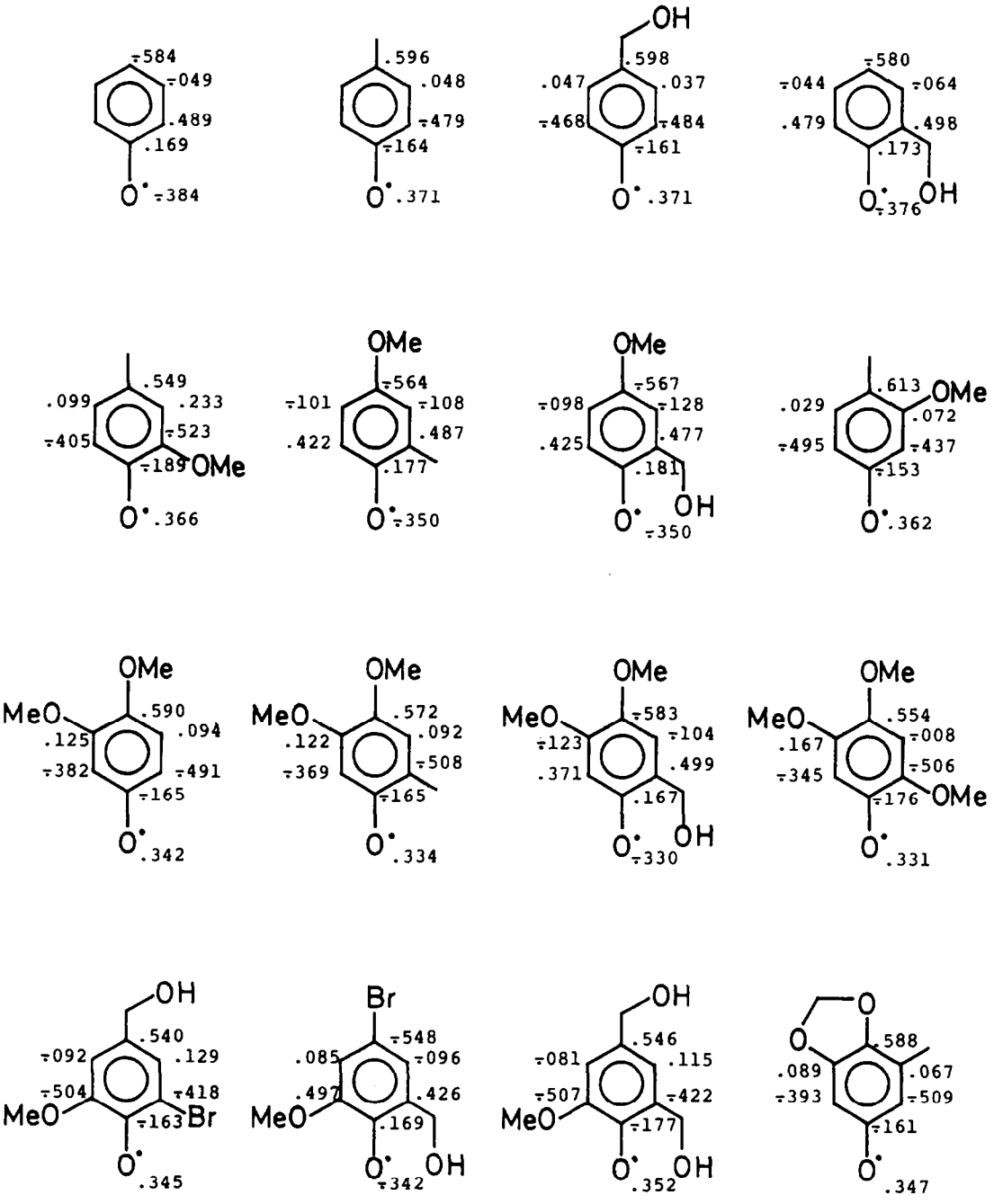
At this point we realized that it would be quite difficult to come up with a rule for predicting the site of F.S. oxidation (ortho vs. ortho' attack) without taking into consideration steric factors. Nevertheless, we hoped that for most cases steric factors would be of no major significance for the regioselective outcome of the reaction[22] and, consequently, could be ignored in a first approximation.

Therefore throughout the second part of the plan we embarked upon executing MO calculations using the MNDO[23] method. More specifically, we employed the "half electron" version of this semiempirical method for calculating meaningful properties of a series of selected phenoxy radicals.

As expected[24], we found that in all cases studied, the electronic pi state of the phenoxy radicals is of the quinoid type, i.e.: large 1,2 and 1,6 bonds, short 2,3 and 5,6 bonds, intermediate 3,4 and 4,5 bonds, and contracted C-O bonds. Besides, calculated spin densities agree reasonably well with those derived from the McConnell equation[25].

Several interesting, though unremarkable, conclusions can be drawn from these MNDO calculations performed throughout this work (meaningful parameters are shown in Scheme 5 and Table 1):

a) the largest SOMO coefficient of the phenoxy radicals studied is always at C-4,


OH
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MeO
Br
O
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.393
.509
.161
.347

Scheme 5

Table 1.- MNDO calculations of phenoxy radicals: Interatomic distances (Å) and Heat of formation (kcal/mol).

Radical	C_1-O$^{\cdot}$	C_1-C_2	C_2-C_3	C_3-C_4	C_4-C_5	C_5-C_6	C_6-C_1	ΔH_f
Phenoxyl	1.240	1.486	1.399	1.424	1.424	1.399	1.486	10.60
4-methylphenoxyl	1.240	1.484	1.396	1.434	1.434	1.396	1.484	2.25
4-hydroxymethylphenoxyl	1.240	1.482	1.399	1.433	1.438	1.395	1.484	-38.62
2-hydroxymethylphenoxyl	1.240	1.497	1.408	1.423	1.423	1.396	1.486	-39.93
2-methoxy-4-methylphenoxyl	1.238	1.499	1.425	1.424	1.437	1.391	1.483	-37.72
2-methyl-4-methoxyphenoxyl	1.238	1.497	1.406	1.436	1.446	1.388	1.484	-38.64
2-hydroxymethyl-4-methoxyphenoxyl	1.239	1.496	1.404	1.438	1.446	1.389	1.483	-81.79
3-methoxy-4-methylphenoxyl	1.240	1.481	1.412	1.458	1.435	1.395	1.481	-34.06
3,4-dimethoxyphenoxyl	1.239	1.481	1.404	1.471	1.435	1.394	1.482	-68.85
2-methyl-4,5-dimethoxyphenoxyl	1.239	1.495	1.406	1.433	1.470	1.402	1.481	-76.06
2-hydroxymethyl-4,5-dimethoxyphenoxyl	1.239	1.499	1.404	1.435	1.469	1.400	1.481	-117.42
2,4,5-trimethoxyphenoxyl	1.235	1.502	1.417	1.429	1.471	1.400	1.480	-109.08
2-methoxy-4-hydroxymethyl-6-bromophenoxyl	1.232	1.505	1.421	1.423	1.438	1.395	1.487	-75.29
2-methoxy-4-bromo-6-hydroxymethylphenoxyl	1.234	1.507	1.417	1.415	1.426	1.404	1.502	-75.97
2-methoxy-4,6-bishydroxymethylphenoxyl	1.235	1.504	1.418	1.423	1.433	1.401	1.495	-130.88
3,4-methylenedioxy-5-methylphenoxyl	1.239	1.490	1.387	1.458	1.425	1.413	1.493	-72.48

thus supporting the contention that coupling with F.S. (and presumably with other radicals as well) must take place at this site.

b) coefficients at C-2 and C-6 are also large, though somewhat smaller than that at C-4. Moreover, on comparing SOMO coefficients at C-4 to those at C-2 and C-6, we came to following remarkable conclusion: F.S. oxidation of phenols with not-easy-to-displace groups at C-4 takes place at the site of the second highest SOMO coefficient (Scheme 5).

To conclude that the observed site of attack by F.S. on simple phenols is mainly dictated by the size of the SOMO coefficients of the corresponding phenoxy radicals is an unavoidable temptation. However, it must be stated that the role played by the SOMO coefficients on determining the regiochemical outcome of the F.S. oxidation of phenols should not be overemphasized. In fact, regioselectivity is, in many cases, hardly predictable due to the finely balanced situation of electronic and steric factors. Consequently it is not advisable to draw definitive conclusions only from MO calculations, in regard with the ortho vs. ortho' regioselectivity.

EXPERIMENTAL PART

All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in a Varian CFT-80A instrument, using tetramethylsilane (TMS) as internal standard and chloroform-d ($CDCl_3$) as solvent, unless stated otherwise. Mass spectra (EI mode) were performed with a Hewlett-Packard 5930-A instrument. IR spectra were recorded with a Hitachi 260-10 instrument.

Fremy's salt (F.S.) was prepared, recrystallized and stored as reported[1]. 4-Substituted-2,6-bishydroxymethyl phenols 1a[26], 1b[27], 1c[28] were prepared as reported. All phenolic benzaldehydes required for the preparation of benzylalcohols 3-15 were used as received (Aldrich, Sigma), except in the case of 2-hydroxy-4,5-dimethoxy benzaldehyde which was prepared from commercial 3,4-dimethoxy phenol as indicated in the literature[29].

MO calculations were performed with a VAX 11/750. The "half electron" version of the semiempirical MNDO method of Dewar et al.[23] was used throughout this work.

Fremy's salt oxidation of 2,6-bishydroxymethyl-4-methoxy phenol 1a

A solution of 0.5 g (2.7 mmol) of 1a[26] in ethyl acetate (50 ml) was added to a buffered solution (Na_2HPO_4, NaH_2PO_4, pH=5.8, 200 ml) of 2.2 g (c.a. 8.2 mmol) of Fremy's salt. Vigorous stirring was mantained during 90 min.. The aqueous solution was then separated and further extracted (salting is recommended) with ethyl acetate. The combined extracts (800 ml) were dried over anhydrous sodium sulphate and the solvent eventually removed under reduced pressure. Crude hydroxymethyl-o-quinone 2a was obtained as a red crystalline material (90% yield), m.p. 118-120 ºC, which tends to decompose even on storage at -40ºC; IR(KBr) 3500, 1680, 1650, 1220 cm^{-1}; ^{1}H NMR 6.89(dt, 1H, J=3.0 and 1.7 Hz), 5.73(d,1H,J=3 Hz), 4.49(d,2H, J=1.7 Hz), 3.86(s,3H); ^{13}C NMR (CD_3COCD_3+D_2O) 179.03, 171.21, 142.70, 133.02, 100.50, 57.21, 57.03; MS(%): 170 (M^++2,9), 168(M^+,27), 152(63), 140(15), 125(30), 124(30) 111(31), 97(27), 81(27), 79(27), 69 (100).

Fremy's salt oxidation of 2,6-bishydroxymethyl-4-methyl phenol 1b

To a stirred solution of 0.3 g (1.78 mmol) of 1b[27] in 75 ml of ethyl acetate, a buffered (Na_2HPO_4, NaH_2PO_4, pH=5.4, 100 ml) solution of Fremy's salt (1.45 g, 5.4 mmol) was added. After three hours of vigorous stirring, the organic phase was separated and the aqueous layer was then further extracted with ethyl acetate. The organic extracts (500 ml) were dried and evaporated under vacuum. The crude residue of hydroxymethyl-o-quinone 2b (0.185 g,67%) crystallized from ethyl acetate as red needles m.p. 77-80°C. The product deteriorates rapidly even when stored at -40°C; IR(KBr) 3500, 1670, 1650 cm^{-1}; ^{1}H NMR 6.88(d,1H,J=1.7 Hz), 6.19(broad s,1H), 4.47 (broad s,2H), 2.16(broad s,3H); MS(%): 154($M+2^+$,4), 152(M^+,100), 151(67), 136(15), 134(15), 123(25), 106(33), 95(20), 77(38), 43(100).

Attempted Fremy's salt oxidation of 2,6-bishydroxymethyl-4-phenyl phenol 1c

To a solution of 0.1g (0.43 mmol) of 1c[28] in 25 ml of ethyl acetate was treated with a buffered solution (Na_2HPO_4, NaH_2PO_4, pH=5.3) of Fremy's salt (0.35g, 1.3 mmol), and the resulting mixture was then vigorously stirred for three hours. Almost no color change was observed after this period of time. Usual workup yielded unchanged starting material 1c in 80-90% yield.

Similar results were obtained by working at pH=7 and pH=4.9 .

Preparation of phenolic benzylalcohols 3, 4, 5, 11, 14. General procedure

To a solution (or suspension) of the ortho (or para) hydroxybenzaldehyde (c.a. 5 mmol) in anhydrous THF (50-100 ml), sodium borohydride (c.a. 5.5mmol) was

added. When the reaction was complete (tlc monitoring) water was added and the solution acidified to pH=2 with 10% HCl. The solution was saturated with NaCl and extracted with chloroform. The extracts were then washed and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure provided crude products of excellent purity (i.e. uncontaminated with byproducts of overreduction, dimerization, etc) in high yield. This method was found particularly useful for the preparation of 5, 11 and 14.
3 m.p. 137-9ºC (lit[30] m.p. 137-9ºC)
4 m.p. 90-2ºC (lit[31] m.p. 91ºC)
5 m.p. 104-6ºC (lit[32] m.p. 106-7ºC)
11 m.p. 78-80ºC (lit[33] m.p. 80-1ºC)
14 m.p. 131-3ºC; ^{1}H NMR 6.25(s,1H), 6.43(s,1H), 4.68(s,2H), 3.76(s,6H)

Fremy's salt oxidation of 2-bromo-4-hydroxymethyl-6-methoxy phenol 3

Fremy's salt oxidation of 3 was carried out under the reported[4] conditions, thus yielding bromoquinone 8 (80%), m.p. 162-3ºC (lit[34] m.p. 161-2ºC); IR(KBr) 1680,1640 cm^{-1}; ^{1}H NMR 7.19(d,1H,J=2 Hz), 5.95(d,1H,J=2 Hz), 3.95(s,3H).

Fremy's salt oxidation of 2-methoxy-4-bromo-6-hydroxymethyl phenol 4

An acetone (6 ml) solution of 4 (0.172 g, 0.74 mmol) was added to a buffered solution (Na_2HPO_4, NaH_2PO_4, pH=5.8) of Fremy's salt (0.6 g, 2.24 mmol). The resulting yellow-brown mixture was stirred for 15 min.. The solution was then saturated with NaCl and extracted with ethyl acetate. The extracts were dried and finally evaporated under vacuum. The residue was identified as 6-hydroxymethyl-2-methoxy-1,4-benzoquinone 9 (65%) m.p. 151-3ºC (lit[35] m.p. 155-155.5ºC); IR(KBr) 3500, 1680, 1650 cm^{-1}; ^{1}H NMR 6.72(dt,1H,J=2.4 and 1.6 Hz), 5.91(d,1H,J=2.4 Hz), 4.56(broad s, 2H), 3.82 (s,3H)

Fremy's salt oxidation of 2-methoxy-4,6-bishydroxymethyl phenol 5

A buffered solution (Na_2HPO_4, NaH_2PO_4, pH=7, 100 ml) of 0.4 g (0.77 mmol) of F.S. was added all at once to a solution of 0.514 g (2.9 mmol) of 5 dissolved in ethanol (5 ml) and chloroform (25 ml). After 5 min. of vigorous stirring the chloroform layer was separated. Fresh chloroform was added and the mixture was then left to stir for another 30 min.. The aqueous phase was then saturated with NaCl and further extracted. On evaporation a residue was obtained which was chromatographed on a short path silicagel column (Et_2O), thus providing 2-methoxy-6-hydroxymethyl-1,4-benzoquinone 9, m.p. 151-3ºC (lit[35] m.p. 155-155.5ºC), in 59% yield.

Fremy's salt oxidation of 2-methoxy-6-hydroxymethyl phenol (orthovanillyl alcohol) 6

Oxidation of 6 was carried out as reported . 2-Methoxy-6-hydroxymethyl-1,4-benzoquinone 9 m.p. 151-3ºC (lit[35] m.p. 155-155.5ºC) was obtained in 78% yield.

Fremy's salt oxidation of 2-methoxy-4-hydroxymethyl phenol (vanillyl alcohol) 7

The Fremy's salt oxidation of 7 under the reported conditions[4] provided methoxy 1,4-benzoquinone 10 m.p. 138-9ºC (lit[37] m.p. 140ºC) in 83% yield.

Fremy's salt oxidation of 2-hydroxymethyl-4-methoxy phenol 11

150 mg (0.97 mmol) of 11 were dissolved in 10 ml of acetone. To this solution Fremy's salt (0.78 g, 2.9 mmol) dissolved in 60 ml of buffer (Na_2HPO_4, NaH_2PO_4, pH=5.8) was added. After 15 min. of vigorous stirring the organic phase was separated and further extracted with ethyl acetate (8x50 ml). The combined extracts were then dried over anhydrous sodium sulphate and evaporated under vacuum. The resulting crude material could not be purified by chromatography since extensive decomposition took place on the column. Washing the crude material several times with ether gave pure 3-hydroxymethyl-5-methoxy-1,2-benzoquinone 2a in 53% yield, m.p. 118-120ºC, identical to that obtained from oxidation of 1a.

Fremy's salt oxidation of 3,4-dimethoxy phenol 13

The oxidation of 13 when carried out under the reported conditions[36] provided 4,5-dimethoxy-1,2-benzoquinone in 80% yield as orange crystals, m.p. 225-6ºC (lit[37] m.p. 225-6ºC); IR(KBr) 1645, 1225 cm^{-1}; ^{1}H NMR 5.75(s,2H), 3.89(s,6H).

Fremy's salt oxidation of 2-hydroxymethyl-4,5-dimethoxy phenol 14

A solution of 0.33 g (1.23 mmol) of F.S. in 60 ml of buffer (Na_2HPO_4, NaH_2PO_4, pH.5.8) was added to a stirred solution (3 ml) of 76 mg (0.41 mmol) of 14. The resulting mixture was stirred for 10 min. and then extracted with chloroform (4x40 ml). The extracts were dried and finally evaporated to dryness, thus yielding 59 mg (85%) of 4,5-dimethoxy-1,2-benzoquinone as an orange crystalline substance m.p. 225-6ºC (lit[37] m.p. 225-6ºC), identical under all respects to that obtained from 13.

Fremy's salt oxidation of 2-methyl-4,5-dimethoxy phenol 15

A solution of 200 mg (1.21 mmol) of 15 in 5 ml of acetone was added dropwise to a stirred solution of 0.97 g (3.63 mmol) of Fremy's salt and 0.22 g of NaH_2PO_4 in 60 ml of water (pH=4.9). Stirring was continued for another four hours, during which the pH dropped to 2.8. The resulting yellow solution was extracted with ether (6x40 ml). The extracts were then washed with water, dried, and finally evaporated to dryness. The residue (110 mg, 60%) crystallized from dioxane-hexane (1:5) yielding 81 mg of an orange crystalline substance m.p. 174-5ºC (lit[38] m.p. 175ºC); IR(CCl_4) 1680, 1650 cm^{-1}; ^1H NMR 6.54(q,1H,J=1.5 Hz), 5.92(s,1H), 3.81(s, 1H), 2.06(d,3H,J=1.5 Hz).

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10.- According to bioreductive alkylation theory, these hydroxymethyl o-quinones might be considered potencial prodrugs. See "The shikimic acid pathway" Ed. Eric E. Conn, Plenum Publishing Co., p.263, 1986, and references therein.

11.- This loosely defined term is meant here to describe those groups which are easily lost (-CH_2OH, -Br, -Cl, -COOH, -$CONH_2$, -CH(OH)CN) during F.S. oxidation of substituted phenols. Strictly speaking, H should also be included in the above list. We have considered it apart just for mere clasification reasons.

12.- a) See for example: J. Wu, J.L. Beal, R.W. Doskotch, J. Org. Chem. 45, 208 (1980); R.C. Donald, J.M. Lansinger, T.S. Lillie, C.J. Wheeler, J. Org. Chem. 47, 2541 (1982). b) W.D. Samuels, D.A. Nelson, R.T. Hallen, Tet. Lett. 27, 3091 (1986); B.J. Arnold, S.M. Mellows, P.G. Sammes, J. Chem. Soc. Perkin Trans. I,1266 (1973); c)"Methoden der Organischen Chemie"(Houben Weyl) Band IV/1d, Teil II, p. 272, Georg Thieme Verlag, Stuttgart, 1981.

13.- See references 4,5 and 6.

14.- As a referee has pointed out, the Fremy's salt oxidative degradation of 2,4-ditertbutyl-6-methyl phenol does not fit into the general rule, as it has been shown to give rise to 3-methyl-5-tertbutyl-1,2-benzoquinone. See R. Magnusson, Acta Chem. Scand., 18, 759 (1964).

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