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HOMOLYTIC ALKYLATION OF NAPHTHOQUINONE AND METHYL-NAPHTHOQUINONE. ENTHALPIC, STERIC AND POLAR EFFECTS.

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Abstract- The homolytic methylation of naphthoquinone to obtain menadione has been investigated by three sources of methyl radical: t-BuOOH, DMSO and H_2O_2, acetone and H_2O_2. Moreover the homolytic alkylation of naphthoquinone and 2-methylnaphthoquinone has been investigated by using alkyl iodides as sources of alkyl radicals.

Menadione (2-methyl-1,4-naphthoquinone, vitamin K_3) is industrially produced by chromic oxidation of 2-methylnaphtalene. Since 1,4-naphthoquinone is a by-product in the industrial production of phthalic anhydride by naphtalene oxidation we have considered the possibility of its homolytic methylation by using simple sources of methyl radical. At the same time we have investigated the general problem of the homolytic alkylation of 1,4-naphthoquinone and 2-methyl-1,4-naphthoquinone by using recent radical sources developed by us[1] from alkyl iodides.

Results and discussion

Homolytic methylation- We have utilized three simple different sources of the methyl radical:

1) t-Butyl hydroperoxide- The methyl radical is formed by β-fission of t-butoxy radical generated by the redox decomposition of the hydroperoxide (eq. 1):

$$Fe^{2+} + \text{t-BuOOH} \longrightarrow Fe^{3+} + OH^- + \text{t-BuO} \xrightarrow{k_1} \text{MeCOMe} + \text{Me} \quad (1)$$

To make eq. 1 effective, it is necessary to minimize the two main competitive reactions of the t-BuO radical, which lead to t-butyl alcohol: hydrogen abstraction from C-H bonds in the reacting system (eq. 2) and reduction by Fe(II) salt (eq. 3):

$$\text{t-BuO} + \text{H-R} \xrightarrow{k_2} \text{t-BuOH} + \text{R} \quad (2)$$

$$\text{t-BuO} + Fe^{2+} + H^+ \longrightarrow \text{t-BuOH} + Fe^{3+} \quad (3)$$

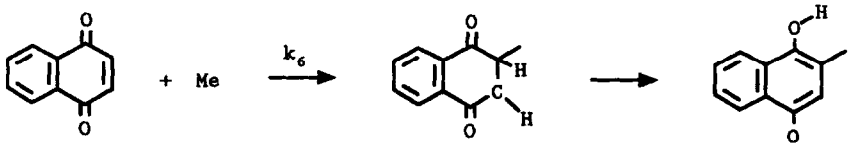
In order to increase the $k_1\backslash k_2$ ratio we took advantage of temperature, solvent and polar effects[1,2]. Refluxing acetic acid or mixtures of acetic acid-water proved to be particularly effective. We have minimized eq. 3 by using catalytic amounts of $Fe(OAc)_2OH$; two redox processes can be considered as the initiation steps of the chain leading to the methylation of 1,4-naphthoquinone: the reduction (eq. 4) and the oxidation (eq. 5) of the Fe(III) salt by t-BuOOH.

$$\text{t-BuOOH} + \text{Fe(III)} \longrightarrow \text{t-BuO}^{\bullet} + \text{Fe(II)} + H^+ \quad (4)$$

$$[>\text{Fe(III)}]^+ + \text{t-BuOOH} \longrightarrow [>Fe^{IV}{=}O] + \text{t-BuO}^{\bullet} + H^+ \quad (5)$$

The reactions (4) and (5) are much slower than the reaction (1) (no reaction occurs at room temperature in the presence of Fe(III) salt, whereas reaction (1) is very fast at 0°C) so that the steady-state concentration of Fe(II) salt remains very low during the reaction.

In this way we have developed a simple and effective source of methyl radical useful for the methylation of 1,4-naphthoquinone. This occurs according to the redox chain, characterized by eqs. 1, 6 and 7.



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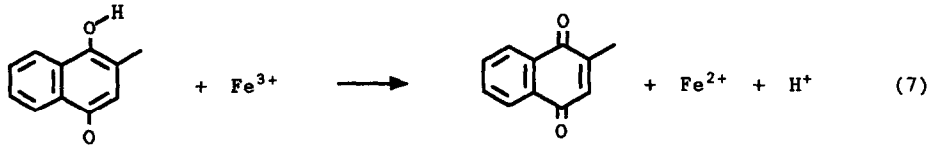

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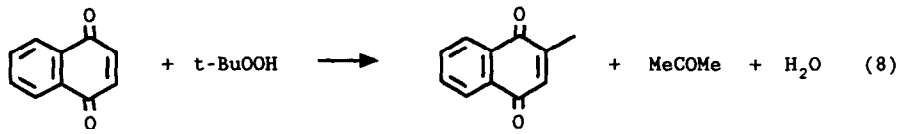
The Fe(II) salt, consumed in eq. 1, is regenerated in eq. (7). The overall stoichiometry is given by eq. (8).

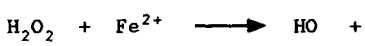


(8)

Reaction (6) is very fast; a value of $k_6 > 10^7$ $M^{-1}s^{-1}$ has been estimated, as it will be shown later, and the main synthetic problem concerns the ratio between mono- and dimethylation. By using an excess of t-BuOOH it is quite easy to obtain 2,3-dimethyl-naphthoquinone. The monosubstitution, however, is not selective because even at partial conversions of naphthoquinone significant amounts of dimethylderivative are formed: the introduction of a methyl group affects to a small extent the reactivity of the quinone ring as the results of Table 1 indicate. Thus either the unfavourable steric and polar effects of the methyl group in the quinone ring are very low or they are balanced by the favourable enthalpic effect due to the formation of a tertiary radical adduct (eq.9):

(9)

ii) DMSO and H_2O_2- The methyl radical is generated by the redox decomposition of H_2O_2 in DMSO solution, according to eqs. 10-12:



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$k_{11} = 7 \times 10^9$ $M^{-1}s^{-1}$ (11)

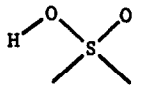
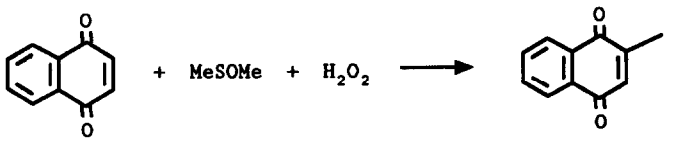


TABLE 1 - Methylation of naphthoquinone by t-BuOOH

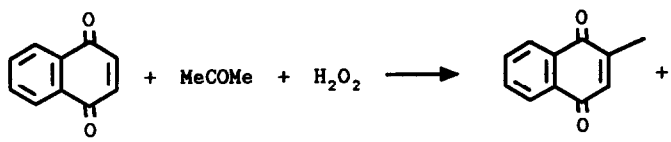
Ratio t-BuOOH / naphthoquinone	Solvent	Conversion %	2-Methyl %	2,3-Dimethyl %
1	AcOH	69	73	27
2	AcOH	100	33	66
0 25	AcOH 4 H_2O 1	18	95	5
0 5	"	45	84	16
1	"	80	75	25
2	"	94	46	54
2	AcOH 1 H_2O 1	100	20	80
1	AcOH 3 H_2O 7	80	65	35
2	"	100	18	82
0 5	H_2O	25	100	-

The high reactivity and the low selectivity of the hydroxyl radical with a large variety of organic and inorganic compounds are controlled by using DMSO as solvent[1]. Also in this case a redox chain, including eqs. 10-12 and 6,7, occurs: the Fe(II) salt, consumed in eq. 10 is regenerated in eq. 7. The overall stoichiometry is shown by eq. 13:



The results are reported in Table 2; the overall yields based on reacted naphthoquinone are in the range of 80-90 %.

iii) Acetone and H_2O_2- The thermal decomposition of H_2O_2 in acetone and catalytic amount of relatively strong acids proved to be an other simple and cheap source of methyl radical, which we have utilized for the methylation of naphthoquinone (eq. 14):



The generation of the methyl radical is due to the thermal decomposition of acetone peroxide (15):

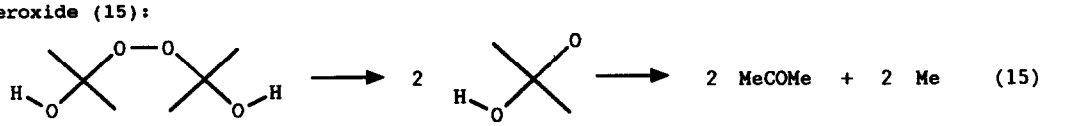


TABLE 2 - Methylation of naphthoquinone by DMSO and H_2O_2

Ratio $\frac{H_2O_2}{\text{naphthoquinone}}$	Solvent	Conversion %	2-Methyl %	2,3-Dimethyl %
0 5	DMSO	43	77	23
1	"	58	33	67
1	DMSO 1 H_2O 1 Toluene 1	53	64	36
1	DMSO 1 H_2O 9 Toluene 1	52	56	44
1	DMSO 1 H_2O 9 Toluene 5	31	66	34

Some degradation of the quinone derivatives occurs and the overall yields based on reacted naphthoquinone are in the range of 40-50% (Table 3).

TABLE 3 - Methylation of naphthoquinone by acetone and H_2O_2

Ratio $\frac{H_2O_2}{\text{naphthoquinone}}$	Acid	Conv.%	2-Methyl%	2,3-Dimethyl%	Yields[a]%
2	CF_3COOH	34	87	13	41
1	H_2SO_4	43	83	17	39
2	"	80	58	42	37
2	$MeSO_3H$	69	86	14	47

a) based on converted naphthoquinone

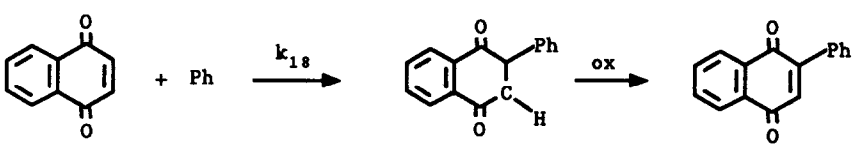
Homolytic alkylation of naphthoquinone and 2-methylnaphthoquinone by alkyl iodides- We[1] have recently shown that the alkyl radicals generated by iodine abstraction from alkyl iodides by aryl (eq. 16) or methyl (eq. 17) radicals can be utilized for selective syntheses:

$$R\text{-}I + Ar \longrightarrow R + Ar\text{-}I \qquad k_{16} > 10^9\ M^{-1}s^{-1} \qquad (16)$$

$$R\text{-}I + Me \longrightarrow R + Me\text{-}I \qquad k_{17} > 10^6\ M^{-1}s^{-1} \qquad (17)$$

We have tried to utilize these radical sources for the homolytic alkylation of naphthoquinone.

At first we have determined the rate constant for the addition of the phenyl radical to 1,4-naphthoquinone by comparison, at low conversions, of the addition of the phenyl radical to the quinone ring (eq. 18) and the iodine abstraction from isopropyl iodide (eq. 19), for which the rate constant is known[3]:



(18)

$$Me_2CH\text{-}I + Ph \xrightarrow{k_{19}} Me_2CH + I\text{-}Ph \qquad k_{19} = 1.27 \times 10^9\ M^{-1}s^{-1} \qquad (19)$$

The isopropylquinone is formed in equimolecular amount with iodobenzene indicating that the isopropyl radical is quantitatively trapped by the quinone ring (Table 4).

TABLE 4 - Relative rates for reactions (18) and (19)

Radical source	naphthoquinone / isopropyl iodide	T°C	2-phenyl-naphthoq mol%	2-isoprpyl-naphthoq mol%	Ph-I mol%
$(PhCOO)_2$	0.5	80	59.2	40.8	42.6
"	1	80	74.4	25.6	26.1
"	2	80	85.3	14.7	15.4
PhN_2^+	0.5	40	58.1	41.9	43.4
"	1	40	73.9	26.1	26.6
"	2	40	84.3	15.7	16.3

The phenyl radical was generated at 40°C from the diazonium salt and Fe(II) salt in DMSO and from benzoylperoxide in benzene at 80°C. From these results a rate constant, $k_{18} = 3.5 \times 10^9\ M^{-1}s^{-1}$ has been evaluated at 40°C. Since the phenyl radical reactions are poorly sensitive to polar effects[4] this high reactivity (3-4 orders of magnitude higher than the addition to simple olefin or benzene ring) must be mainly ascribed to the enthalpic effect connected with the energies of the bonds involved and the stability of the radical adduct.

TABLE 5 - Alkylation of 2-methyl-naphthoquinone by alkyl iodides and $(PhCOO)_2$ or p-chlorobenzendiazonium fluoborate

Radical source	R-I	Conversion %	3-alkyl %	3-aryl %
$(PhCOO)_2$[a]	c-C_6H_{11}[a]	91	32	68
$(PhCOO)_2$	c-C_6H_{11}	83	92	8
"	n-Bu	68	87	13
"	i-Pr	93	94	6
"	i-Pent	88	93	7
p-Cl-C_6H_4-N_2^+[a]	c-C_6H_{11}[a]	68	26	74
"	"	63	86	14
"	n-Bu	54	82	18
"	i-Pr	71	88	12
"	t-Bu	84	96	4

a)-Quinone and cyclohexyl iodide were dissolved in benzene before the reaction

Thus, as the results of Table 5 and 6 indicate, significant amounts of alkyl and phenyl derivatives are obtained by using equimolecular ratios of alkyl iodides and naphthoquinones; from practical point of view a good selectivity was obtained by slow addition of the quinone during the reaction so that its stationary concentration in the reaction medium is low compared to the alkyl iodide concentration.

TABLE 6 - Alkylation of naphthoquinone by alkyl iodides and $(PhCOO)_2$ or p-chlorobenzendiazonium fluoborate

Radical source	R-I	Naphthoq rad / source	Conv %	3-alkyl%	3-aryl%	2,3-di-subst %
$(PhCOO)_2$	c-C_6H_{11} [a]	1	78	22	38	40
"	c-C_6H_{11}	1	76	45	5	50
"	"	0 5	38	85	4	11
"	n-Bu	0 5	36	76	7	17
"	i-Pr	0 5	41	87	4	9
ArN_2^+	t-Bu	1	82	87	8	5

a)-Quinone and cyclohexyl iodide were dissolved in benzene before the reaction

We have determined by the competitive method the relative rates of the reactions of naphthoquinone and 2-methyl-naphthoquinone with n-butyl and isopropyl radicals. The results, reported in Table 7, show that there is no substantial difference in reactivity with n-butyl radical; with isopropyl radical naphthoquinone is about 1.5 times more reactive than 2-methylnaphthoquinone and that, in our opinion, is due more to steric than to polar effect. These results confirm the fact that either the steric and polar effects of the methyl group in the quinone ring are very low or they are balanced by the enthalpic effect, which plays the main role in determining the high rate constants for the addition of the alkyl radicals to the quinone ring[5].

TABLE 7 - Relative rates for the addition of n-Bu and i-Pr radicals to naphthoquinone and 2-methyl-naphthoquinone

Radical	naphthoquinone / 2-methylnaphthoquinone	2-alkyl-naphthoq	2-metyl-3-alkyl-naphthoq
n-Bu	0 5	35 3	64 7
"	1	51 5	48 5
"	2	68 1	31 9
i-Pr	0 5	41 6	58 4
"	1	59 8	41 2
"	2	75 1	24 9

Also with methyl radical it is necessary to keep low the stationary concentration of the quinone during the reaction compared to the alkyl iodide concentration in order to have a

good selectivity of alkylation. The results obtained with t-BuOOH and DMSO as source of methyl radical are shown in Table 8-10.

TABLE 8 - Alkylation of 2-methyl-naphthoquinone by alkyl iodides and t-BuOOH

R-I	t-BuOOH / quinone	Conversion %	2-Methyl-3-alkyl %	2,3-dimethyl %
n-Bu[a]	1	48	39	61
"[a]	2	84	37	63
"[b]	1	52	65	35
"[b]	2	86	87	13
i-Pr[a]	2	94	45	55
"[b]	2	92	92	8
i-Pent[b]	2	90	95	5
c-C_6H_{11}	2	94	93	7

In all cases 5 mol of alkyl iodide for mole of quinone were utilized
a)All the reagents were mixed before the reaction
b)t-BuOOH and the quinone were simultaneously dropped to the mixture of the other reagents

TABLE 9 - Alkylation of 2-methyl-naphthoquinone by alkyl iodides, DMSO and H_2O_2

R-I (mole)[a]	H_2O_2 / quinone	Conversion %	2-Methyl-3-alkyl %	2,3-di-methyl %
n-Bu(1)[b]	1	75	9 8	90 2
(5)[b]	1	76	35	65
" (10)[b]	1	78	52	48
(3)[c]	1 5	87	74	26
i-Pr(5)[b]	1	82	81	19
(3)[c]	1 5	92	87	13
(10)[c]	1 5	100	98	<2
i-Pent(3)[e]	1 5	89	85	15
(3)[c]	2 5	100	84	16
(10)[c]	2	100	>98	traces
t-Bu(3)[d]	1 5	92	83	17
(10)[d]	2	100	>98	traces

a) Mol of alkyl iodide for mole of quinone
b) H_2O_2 was dropped to the mixture of other reagents
c) H_2O_2, quinone and t-Bu-I were simultaneously dropped to $FeSO_4$ in DMSO

TABLE 10 - Alkylation of naphthoquinone by alkyl iodides, DMSO and H_2O_2

R-I (mole)[a]	H_2O_2 / quinone	Conv %	2-Alkyl %	2-Methyl %	2,3-di-substitued %
i-Pr(10)[b]	1	76	79	10	11
" (10)[b]	3	100	27	-	73
" (5)[c]	1	96	87	4	9
i-Pent(5)[c]	1	89	85	5	10
c-C_6H_{11}[c]	1 5	100	78	3	19
t-Bu[d](5)	1 5	100	81	7	12

a) Mol of alkyl iodide for mole of quinone.
b) H_2O_2 was dropped to the mixture of other reagents
c) H_2O_2 and naphthoquinone were dropped to the mixture of other reagents
d) H_2O_2, naphthoquinone and t-Bu-I were simultaneously added to $FeSO_4$ in DMSO

From these results a rate constant > 10^7 $M^{-1}s^{-1}$ can be evaluated for the addition of the methyl radical to naphthoquinone. This again suggests that the enthalpic effect is an important factor, which influence the reactivity of carbon-centered radicals towards the quinone ring. That is in clear-cut contrast with the behaviour of the same radical sources with substrates bearing a positive charge, such as protonated heteroaromatic bases and diazonium salts[1], in which the polar effect is far prevalent and it determines a much higher selectivity of alkylation.

Experimental

All the naphthoquinone derivatives were commercial products or they were prepared according to the literature procedures by alkylation of naphthoquinone with carboxylic acids and lead tetracetate[9] or peroxydisulphate[10] or acyl peroxides [11]. They were utilized for the analysis of the reaction products by g.l.c.

Methylation of naphthoquinone with t-BuOOH

3 mmol of naphthoquinone and 0.3 mmole of $Fe(OAc)_2OH$ were refluxed with t-BuOOH in 25 ml of AcOH-H_2O (in the amounts indicated in Table 1) for 6 h. When only water was utilized as solvent the reaction was carried out at 75°C for 12 h. The solution was diluted with water, extracted with CH_2Cl_2 and analyzed bu g.l.c. (2-cyclohexyl-naphthoquinone as internal standard). The results are reported in Table 1.

Methylation of naphthoquinone by DMSO and H_2O_2

H_2O_2 (30%) was added dropwise over 5 min at room temperature to 3 mmol of naphthoquinone and 0.6 mol of $FeSO_4$ in 20 ml of DMSO, water and toluene in the ratios indicated in Table 2. The solution was stirred for 15 min, diluted with water, extracted with CH_2Cl_2 and analyzed by g.l.c.. The results are reported in Table 2.

Methylation of naphthoquinone by acetone and H_2O_2

H_2O_2 (60%), 3 mmole of naphthoquinone and 5 mmol of acid, as indicated in Table 3, in 25 ml of actone were refluxed for 12 h. The solution was diluted with water, extracted with CH_2Cl_2 and analyzed by g.l.c.. The results are reported in Table 3.

Relative rates of the phenyl radical for the addition to naphthoquinone and iodine abstraction from isopropyl iodide.

i) Benzoyl peroxide as source of phenyl radical.

5 mmol of naphthoquinone and isopropyl iodide in the ratios reported in Table 4 were refluxed with 1 mmol of benzoyl peroxide in 30 ml of benzene 2 h. The solution was directly analyzed by g.l.c. by using 2-methyl-naphthoquinone as internal standard. The results are reported in Table 4.

ii) Benzendiazonium fluoborate as source of phenyl radical.

1 mmole of benzene-diazonium fluoborate in 5 ml of DMSO was added dropwise with stirring over 15 min to 5 mmol of naphthoquinone and isopropyl iodide (in the ratios reported in Table 4) and 1 mmol of $FeSO_4.H_2O$ in 20 ml of DMSO at 40°.The solution was stirred for further 15 min, diluted with water, extracted with CH_2Cl_2 and analyzed by g.l.c. The results are reported in Table 4.

Alkylation of 2-methyl-naphthoquinone by alkyl iodides-

i) Benzoylperoxide as radical source.

A solution of 2-methyl-naphthoquinone (3 mmol) and benzoyl peroxide (3 mmol) in 10 ml of benzene was added dropwise over 2h to a refering solution of alkyl iodide (6 mmol) in 15 ml of benzene. The solution was refluxed for further 30 min and directly analyzed by g.l.c. by using 2-isopropyl-naphthoquinone as internal standard. In one experiment all the reagents were dissolved in benzene and refluxed for 2.5 h. The results are reported in Table 5.

ii) Diazonium salt as radical source.

2-methyl-naphthoquinone (3 mmol) and p-chlorobenzenediazonium fluoborate (3 mmol) in 10 ml of DMSO was added dropwise over 30 min to a stirred mixture of alkyl iodide (6 mmol) and $FeSO_4.7H_2O$ (1.5 mmol) in 15 ml of DMSO at 40°C. The mixture was stirred for further 10 min, diluted with water, extracted with CH_2Cl_2 and analyzed by g.l.c. The results are reported in Table 5.

iii) t-BuOOH as radical source.

2-Methyl-naphthoquinone (3 mmol) and t-BuOOH (3 mmol) in 10 ml of acetic acid was added dropwise to a refluxing solution of alkyl iodide (9 mmol) and $Fe(OAc)_2OH$ (0.6 mmol) in 15 ml of acetic acid over 2 h. The solution was refluxed for further 30 min, diluted with water, extracted with CH_2Cl_2 and analyzed by g.l.c. In one experiment all the reagents were dissolved in acetic acid and refluxed for 2.5 h. The results are reported in Table 8.

iv) DMSO and H_2O_2 as radical source.

H_2O_2 (60%) (6 mmol) in 5 ml of DMSO and 2-methyl-naphthoquinone (3 mmol) in 8 ml of DMSO were simultaneously added dropwise to a stirred mixture of alkyl iodide (9 mmol) and $FeSO_4.7H_2O$ (1 mmol) in 15 ml of DMSO at room temperature over 30 min. THe mixture was stirred for additional 5 min, diluted with water, extracted with CH_2Cl_2 and analyzed by

g.l.c. The results are reported in Table 9.

All the alkyl naphthoquinones were identified by comparison with authentic samples prepared by known procedures[8,9].

Alkylation of 1,4-naphthoquinone by alkyl iodides.

The same methods i-iv were utilized with naphthoquinone with the only difference of utilizing less radical source (1.5 mmol of benzoyl peroxide, diazonium salt and t-BuOOH and 3 mmol of H_2O_2) in order to minimize the extent of disubstitution. The results are reported in Table 6-10.

Relative rates of n-butyl and isopropyl radicals for the addition to naphthoquinone and 2-methylnaphthoquinone.

The procedure i) was utilized, with the difference that only 0.1 mol of benzoyl peroxide was used for mole of quinone in order to keep low the conversions and make suitable the competitive method. The results are reported in Table 7.

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