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SYNTHESIS OF UBIQUINONE AND MENAQUINONE ANALOGUES BY OXIDATIVE DEMETHYLATION OF ALKENYLHYDROQUINONE ETHERS WITH ARGENTIC OXIDE OR CERIC AMMONIUM NITRATE IN THE PRESENCE OF 2,4,6-PYRIDINE-TRICARBOXYLIC ACID

L. Syper, K. Kloc and J. Mizochowski*
Institute of Organic and Physical Chemistry, Technical University 50 370 Wrocław, Poland

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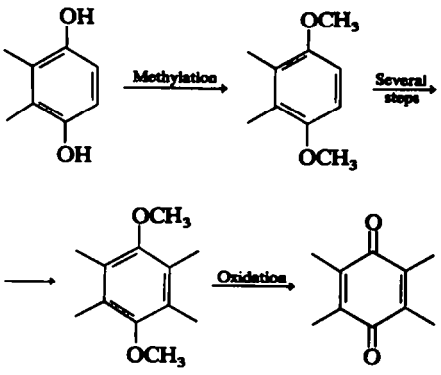
Abstract—It was found that alkenylhydroquinone ethers demethylated with argentic oxide or ceric ammonium nitrate in the presence of 2,4,6-pyridinetricarboxylic acid as a catalyst and afforded ubiquinone-2, menaquinone-2 and their analogs in yields of 53 to 89%. The new approach to the synthesis of starting alkenylhydroquinone ethers as well as 2,4,6-pyridinetricarboxylic acid and its derivatives has been reported.

Oxidative demethylation of hydroquinone dimethyl ethers is a key synthetic reaction used to obtain a variety of quinones.[1-6] Many of them occur in nature, particularly as mena-, plasto- and ubiquinones, and their preparation is important in organic syntheses.[7,8] The synthesis of quinones consists in methylation of hydroquinones, introducing desired substituents and demethylation with simultaneous oxidation as the last step. The method is represented by Scheme 1.



Scheme 1

The oxidation of 1,4-dimethoxyarenes to the corresponding quinones may be accomplished sometimes by fairly concentrated nitric acid. This method is confined to the synthesis of rather simple quinones.[9] A more convenient method is oxidation with argentic oxide (AgO) and this has been used to obtain chlorobiumquinone[10] and menaquinones[11] in high yields but it is not applicable to the preparations of a broad group of alkenylquinones. Intermolecular condensation, side-chain isomerisation as well as chromenyl cyclisations can occur as side reactions and are caused by the high acidity of the reaction mixture.

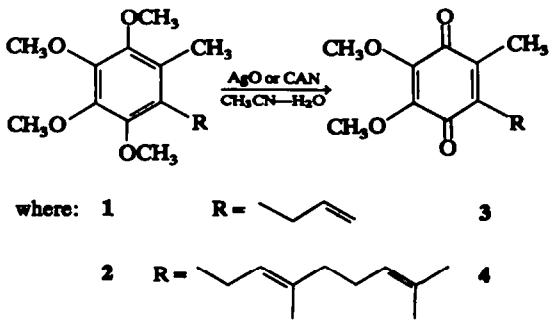
Recently a new method of oxidative demethylation of hydroquinone dimethyl ethers with ceric ammonium nitrate (CAN) has been reported,[12] but its usefulness in the synthesis of alkenylquinones has not been recognised.

Continuing our investigations,[13,14] we have found that oxidative demethylation of hydroquinone ethers is more efficient when pyridine or pyrazinecarboxylic acids having carboxylic groups in α-position are used as catalysts. In this case the reaction is carried out in the presence of a weak organic acid only. It is generally a fast reaction requiring a short time and low temperature (0–2°). We have also observed that, when azinedicarboxylic acids are used, the yields of quinones are higher than in the case of azinemonocarboxylic acids. The presence of a third carboxylic group in the pyridine ring, as in the case of 2,4,6-pyridinetricarboxylic acid (PTA), further improved the yields of quinones and this compound seems to be the best catalyst so far investigated in our laboratory.

The mode of action of the azinecarboxylic acids is probably due to their ability to complexing Ag(II) or Ce (IV). As a result, an electron transfer between an organic molecule and the metal cation becomes easier. It is known that these acids are very efficient catalysts in the electron transfer processes between metal cations.[15-19] We have found that they are also very efficient catalysts in electron transfer from organic molecule to the metal cations.

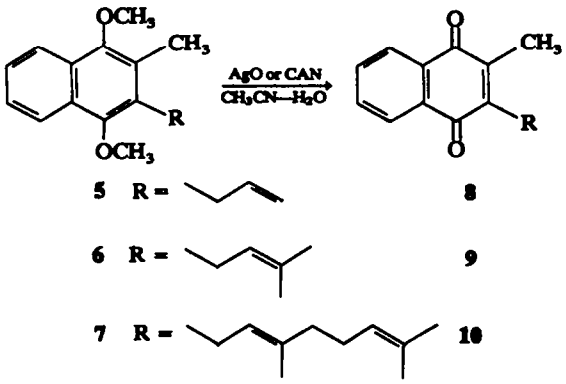
The oxidative demethylation was carried out on two 1-alkenyl-2-methyl-3,4,5,6-tetramethoxybenzenes (**1** and **2**) and on three 2-alkenyl-3-methyl-1,4-dimethoxynaphthalenes (**5**, **6** and **7**). This pattern of substitution is typical for ubiquinones and menaquinones.

The results of the oxidative demethylation of the compounds listed above in the presence of PTA are given in the Table. AgO is completly unreactive without PTA contrary to CAN which acted effectively also when catalyst was not added to the reaction mixture. From the Table, one can see that CAN is not an inferior reagent compared to AgO,



Scheme 2

in the oxidative demethylation of *p*-dimethoxy derivatives of benzene and naphthalene. The yields are comparable and in several instances somewhat higher. The presence of PTA in the mixture, when CAN is used, has little effect on the yields. In the case of an AgO-PTA system, the acidity of the reaction medium is much lower than in the case of CAN itself or CAN-PTA. However, when CAN or CAN-PTA are used, the product isolation is much easier because no insoluble material is present in the mixture. No isomerisation or chromenyl cyclisation was observed, and the method is acceptable as a general one for the preparation of alkenyl-1,4-quinones.



Scheme 3

During our investigation, two additional problems had to be solved i.e. the preparation of pure PTA and the synthesis of alkenyl-1',4-dimethoxyarenes.

In spite of several papers[20] on the synthesis of PTA no convenient and reproducible method of preparation of the pure compound has been reported and its physical properties remain ambiguous. Our experiments have shown that PTA can be easily obtained by oxidation of 2,4,6-collidine with potassium permanganate and the product may be purified by several ways.

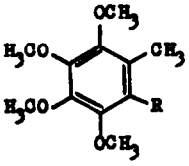
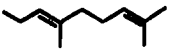
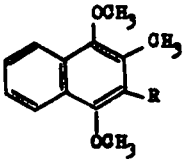
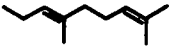
The crude acid was converted into trimethyl ester, which was purified, hydrolysed and the resulting acid recrystallised from dilute hydrochloric acid. This crude acid was converted into hydrochloride by treatment with hot hydrochloric acid (1:1), the hydrochloride decomposed to pure PTA when it was dissolved in water.

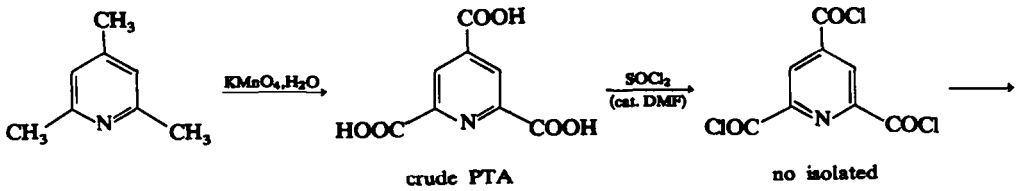
For further characterisation of the acid, we prepared its N-oxide **14** by using 30% hydrogen peroxide in the presence of sodium tungstate under the conditions described.[21] We also prepared 2,4,6-pyridinetrimethylcarboxylate N-oxide **15**. This compound was recently synthesised by cyclisation of aliphatic nitro-compounds.[22]

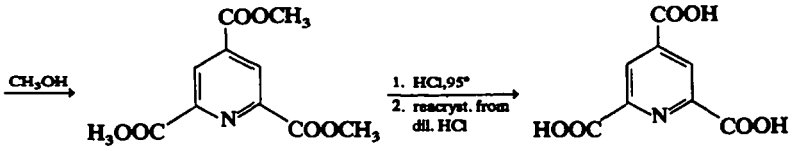
The N-oxide **14** was also tested as catalyst of the oxidative demethylation but no significant improvement of the yields as compared with PTA was observed.

The main substrate for the synthesis of 1-alkenyl-2-methyl-3,4,5,6-tetramethoxybenzenes (**1** or **2**) as well as ubiquinones is 1-methyl-2,3,4,5-tetramethoxybenzene (**22**). Synthesis of this compound was achieved according to Scheme 6:

Table. Results of oxidative demethylation of p-dimethoxyderivatives of benzene and naphthalene

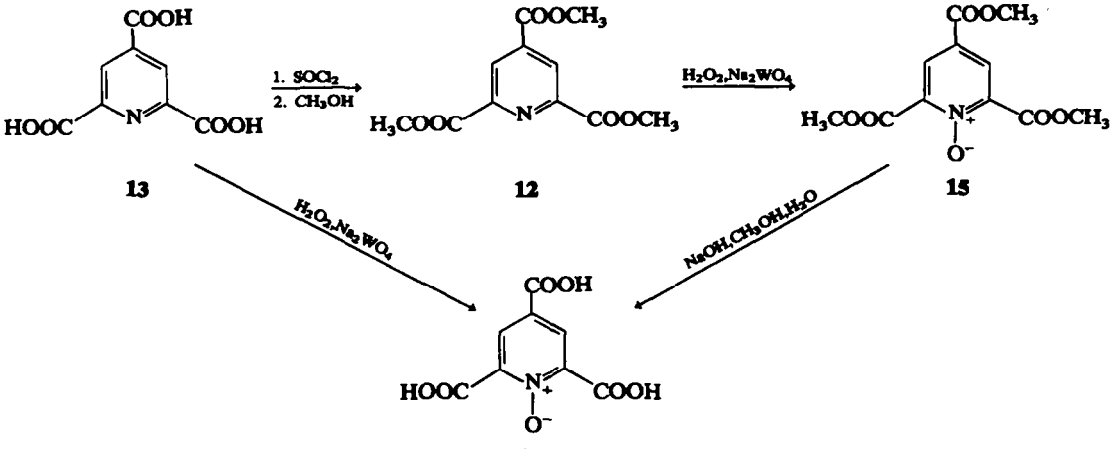
Substrates			Yields of p-quinones, %		
No	Ring system	R	AgO+PTA	CAN	CAN+PTA
1		R = 	61	56	89
2		R = 	77	82	87
5		R = 	84	83	86
6		R = 	79	70	77
7		R = 	45	50	53



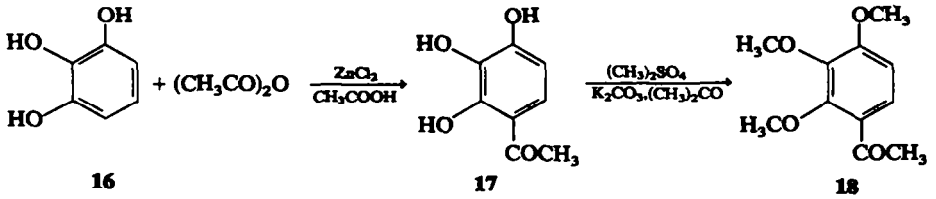


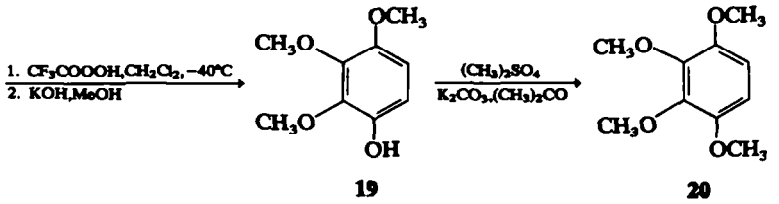
12 13

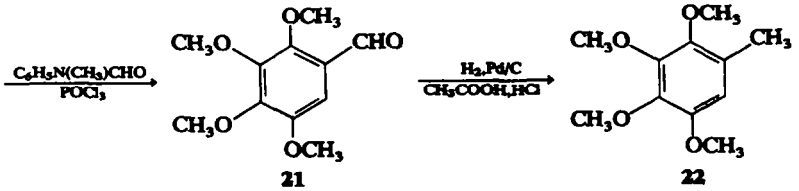
Scheme 4



Scheme 5



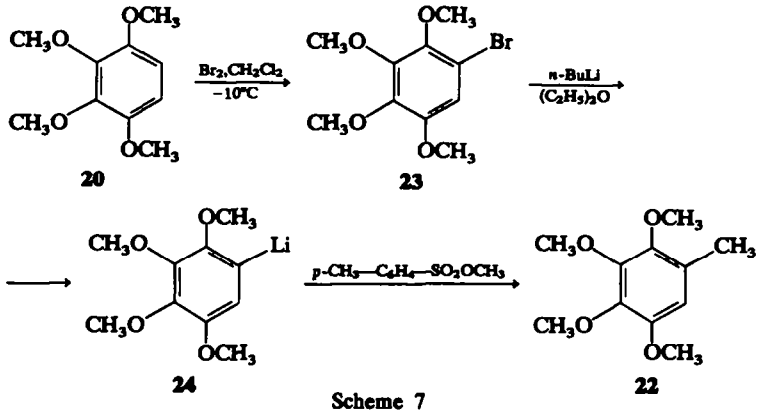




Scheme 6

The tetramethoxybenzene **20** was obtained using our original method, simpler and more effective than any previously reported.[23,24]

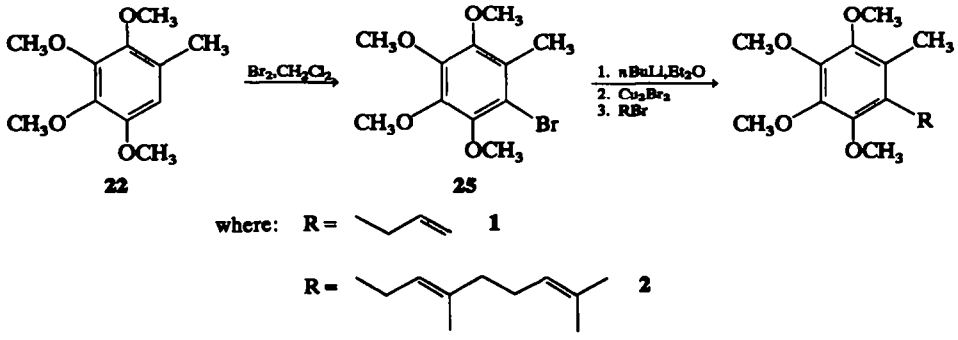
We also proved the alternative method of synthesis of **22** starting from **20**, as shown in the following Scheme:



Scheme 7

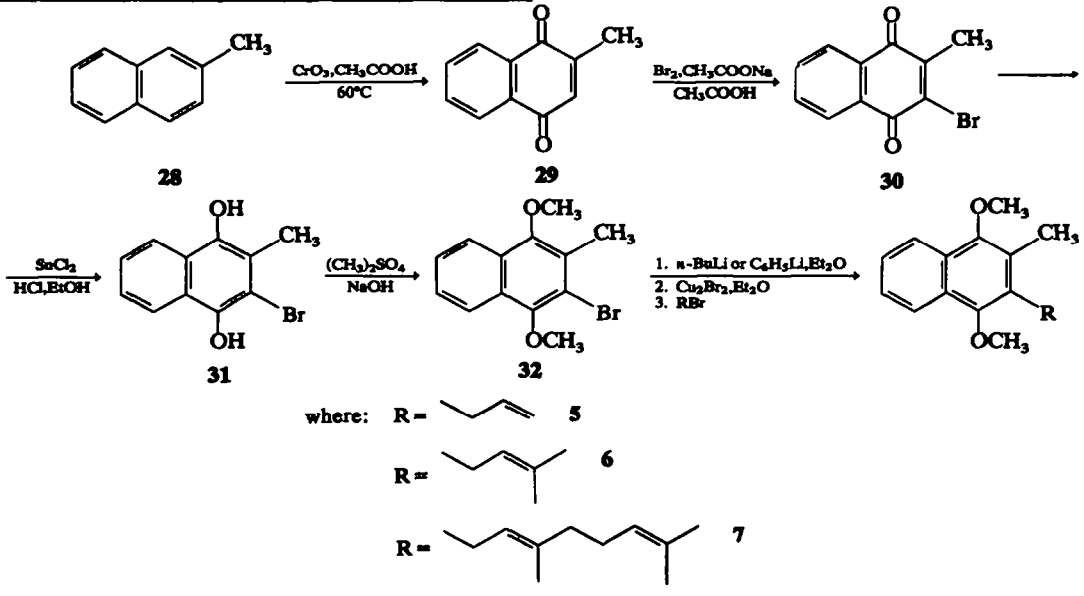
It is difficult to decide which of these two procedures is better. The product **22** obtained by the first method may be purified more conveniently than the product obtained by the second method. The compound **22** obtained by the second method was always contaminated by small amounts of starting **20**, which was formed by reduction of **23**.

The alkenylic substituents were introduced according to the following Scheme:



Scheme 8

2-Alkenyl-3-methyl-1,4-dimethoxynaphthalenes (**5**, **6** and **7**) were synthesised starting from 2-methylnaphthalene according to the following Scheme:



Scheme 9

EXPERIMENTAL

Mps are uncorrected. ^{1}H NMR spectra were recorded on a Tesla apparatus BS-478 (80 MHz) in $CDCl_3$ using HMDS as external standard. IR spectra were obtained with a Perkin-Elmer 621 spectrophotometer.

General procedure for the oxidation of hydroquinone ethers with AgO. To a hydroquinone ether (0.004 mole) soln, in a mixture of acetonitrile (28ml) and water (12 ml) with suspended PTA (4.75 g, 0.02 mole), argentic oxide (2.46 g, 0.02 mole) was added slowly while efficiently stirred and cooled in an ice/water bath. When the addition was complete (30 min), the mixture was diluted with water and insoluble material was filtered off by suction. The solid was thoroughly washed with CH_2Cl_2. The same solvent was used for extraction of the filtrate. The organic extract was washed with water, dried over $MgSO_4$ and the solvent was removed on a rotatory evaporator. The crude quinones were purified by column chromatography packed with silica gel and CH_2Cl_2 was used as an eluent.

General procedure for the oxidation of hydroquinone ethers with CAN. To a hydroquinone ether (0.008 mole) soln in a mixture of acetonitrile (28 ml) and water (12 ml) with suspended PTA (4.22 g, 0.02 mole), a cooled soln of CAN (10.96 g, 0.02 mole) in a mixture of acetonitrile (20 ml) and water (20 ml) was added dropwise for about 20 min. The mixture was cooled in an ice/water bath and stirred when the addition was complete for an additional 20 min. The bath was removed and after 10 min the mixture was poured into a separatory funnel containing 40 ml of water, then extracted several times with CH_2Cl_2. The combined extracts were washed with water, dried over $MgSO_4$ and the quinone was isolated as above.

2,4,6-Pyridinetricarboxylic acid (**13**)

To 121 g (1 mole) of 2,4,6-trimethylpyridine and 2 l of water, $KMnO_4$ (1250 g, 8 mole) was added in 100 g portions during 2 hr intervals at 20–30°.

After addition of the total amount of $KMnO_4$, the reaction was continued for 14 hr at room temp and an additional 15 hr at 45–50°. The ppt of MnO_2 was filtered off and washed several times with hot water. The colourless filtrate was concentrated *in vacuo* to a volume of about 1 l and acidified with conc HCl to pH 2. After cooling the crude ppt was filtered off and washed three times with cold water, and then added to 1 l of water. The suspension of 2,4,6-pyridinetricarboxylic acid was heated to about 95° and HCl was added in small portions (in total amount 70 ml) until almost all the material was dissolved. The hot soln was filtered and allowed to stand for 3 days at 0–5°. The white solid was collected, washed with cold water and dried *in vacuo* over NaOH pellets and P_2O_5 to yield 83.5 g of the product. The washings and the filtrate were concentrated *in vacuo* to about 700 ml and NaOH (17 g, 0.43 mole) in 60 ml of water was added, warmed to boiling and immediately filtered. After identical treatment an additional crop of 31.7 g of the product was obtained. The total yield of the product was 54.5% (115.2 g). This product was considered as crude 2,4,6-pyridinetricarboxylic acid.

2,4,6-Pyridinetrimethylcarboxylate **12**

Method A. The mixture of crude acid **13** (21 g, 0.1 mole), $SOCl_2$ (100 ml) and DMF (1 ml) was refluxed until it became homogeneous (2 hr). The excess of $SOCl_2$ was removed *in vacuo* and 80 ml of MeOH was added slowly. The mixture was refluxed for 1hr, cooled and the crystalline product separated by filtration and washed with cold MeOH. After recystallisation from toluene, 11.3 g (45.0%) of pure **12** was obtained, m.p. 161° (lit.[20] 154.5°). IR (KBr): 1740 cm^{-1} ($\nu_{C=O}$).

Method B. The crude acid (17.4 g, 0.082 mole) was added to 100 ml of MeOH saturated with gaseous HCl and allowed to stand for 10 days at room temp. After this period, water (100 ml) was added and the crystalline product collected by filtration, and dried to yield 14.4 g m.p. 155–160°. Upon recrystallisation from toluene 14.2 g (68.5%) of pure **12** was obtained.

Hydrolysis of 2,4,6-pyridinetrimethylcarboxylate. The pure **12** (17.0 g, 0.067 mole) was heated on a stream bath with 30 ml H_2O and 30 ml of conc, HCl until dissolution was complete (about 1 hr). After cooling to room temp, the soln was neutralised with NaOH to pH about 2. The ppt was filtered off, washed with cold water and redissolved in 70 ml of boiling water with 5.5 ml of conc, HCl. The soln was left to cool and the product collected by filtration, washed four times with cold water, dried *in vacuo* over NaOH pellets and P_2O_5 to yield 12.7 g (89.5%) of pure **13**. This compound does not change when heated in a capillary to 350°. It is soluble in dilute strong acids (HCl, HNO_3, H_2SO_4, and $HClO_4$). We did not obtain consistent analytical data for it by the combustion method. The crystalline acid **13** reveals in the IR (KBr) spectrum three kinds of OH groups: 3620 cm^{-1} (ν_{OH} free), 3422 cm^{-1} (ν_{OH} weakly bonded), broad diffused absorption bands with maxima 2900 and 2500 cm^{-1} (ν_{OH} strong bonded) as well as 1718 cm^{-1} ($\nu_{C=O}$).

Preparation of hydrochloride of (**13**)

Method A. The crude acid **13** (33.0 g, 1.56 mole) and glacial AcOH (150 ml) was heated to boiling and conc. HCl was added in small amounts until dissolution was nearly complete (total 25 ml of HCl).The hot soln was filtered and cooled. The ppt was collected, washed with AcOH and dried *in vacuo* over NaOH pellets and P_2O_5 to give 34.4 g (89%) of monohydrochloride of **13**. The hydrochloride could be recrystallised from 6 N HCl. We did not obtain consistent analytical data for it by the combustion method. It did not change when heated in a capillary to 350°. It is soluble in water but the free acid soon precipitates. IR (KBr): 3462 cm^{-1} (ν_{OH} weak bonded), broad diffused absorption bands with maxima 2920 and 2500 cm^{-1} (ν_{OH} strong bonded, 1722 cm^{-1} ($\nu_{C=O}$).

Method B. The crude acid **13** (10.0 g) was dissolved in hot 6N HCl (25 ml). After cooling to 5°, the hydrochloride precipitated and was collected by filtration, washed with 6N HCl and dried as above to yield 10.0 g (86%).

2,4,6-Pyridinetricarboxylic acid N-oxide (**14**). A suspension of **13** (4.22 g, 0.02 mole) in 30% H_2O_2 (25 ml) with $Na_2WO_4 2H_2O$ (0.2 g) was heated at 95–100° with vigorous stirring for 3hr, then 15 ml of 30% H_2O_2 was added and the mixture heated for an additional 2 hr. After this period the mixture was allowed to stand at 0° and the crystalline crude product was filtered off and washed with small portions of water and MeOH. The filtrate was evaporated near to dryness *in vacuo*, about 10 ml of water was added and an additional amount of crude crystalline product was obtained. Both portions of crude **14** were recrystallised from MeOH and water (1:1) to give 3.5 g (79%) of white crystaliine **14**, m.p. (dec) 179–2811°. IR (KBr): 1710 cm^{-1} ($\nu_{C=O}$), 1265, 1285 cm^{-1} ($\nu_{N\to O}$). (Found: C, 42.15; H, 2.32; N, 6.20. Calc. for $C_8H_5NO_7$, C, 42.30; H, 2.22; N, 6.17%).

2,4,6-Pyridinetrimethylcarboxylate N-oxide (**15**). A suspension of **12** (5.06 g, 0.02 mole) in 30% H_2O_2 (25 ml) with $Na_2WO_4 \cdot 2H_2O$ (0.2 g) was heated at 95-100° with vigorous stirring for 3 hr, then 40 ml of 30% H_2O_2 was added and the mixture heated for additional 2 hr. After this period the mixture was allowed to stand at room temp and the crystalline crude product was filtered off and washed with small portions of water and MeOH. Recrystallisation of the crude N-oxide from MeOH-water gave 3.0 g (56%) of white crystalline **15**, m.p. 130–131° (lit.[22] 109°). IR (KBr): 1740 cm^{-1} ($\nu_{C=O}$), 1280, 1240 cm^{-1} ($\nu_{N\to O}$) (Found: C, 49.19; H, 4.04; N, 5.32. Calcd. for: $C_{11}H_{11}NO_7$, C, 49.07; H, 4.12, N, 5.20%).

Hydrolysis of **15** *to* **14**. Compound **15** (2.69 g 0.01 mole) was suspended in a soln of NaOH (2.4 g, 0.06 mole) in MeOH (25 ml) and water (25 ml) and refluxed until all solid dissolved (about 24 hr). The mixture was then concentrated *in vacuo* to a volume of about 20 ml and acidified with conc HCl to pH 3–4. The crude ppt was collected and recrystallised from MeOH-water (1:1) to give pure **14** (1.1 g, 48%).

2,3,4-*Trimethoxyacetophenone* (**18**). a mixture of **17** (obtained in accordance with lit.[25]) (45.8 g, 0.27 mole), K_2CO_3 (220 g, 1.6 mole), dimethyl sulphate (80 ml, 0.85 mole) and acetone (600 ml), was refluxed for 24 hr. Acetone was distilled off and water was added to the residue. The product was isolated by the ether extraction and vacuum distillation to yield 51.5 g (90.5%) of **18**, b.p. 176° (15 mm) Lit.[26] 185° (20 mm).

2,3,4-*Trimethoxyphenol* (**19**). To a stirred mixture of CH_2Cl_2 (300 ml) and 75% H_2O_2 (27.0 g, 0.59 mole) trifluoroacetic anhydride (80 g, 0.38 mole) was added dropwise at −30 to−25°. The stirring was continued for 20 min. at −30° after the addition and the temp was lowered to −40°. A soln of **18** (63.0 g, 0.30 mole) in CH_2Cl_2 (60 ml) was added dropwise under N_2. The mixture was stirred at −40° for an additional 20 min, and the cooling bath was removed and the mixture was allowed to warm up to room temp. After three washings with water saturated with $NaHCO_3$, then with water alone and drying over Na_2SO_4, the solvent was removed *in vacuo*. To the oily residue, a soln of KOH (40 g) in MeOH (300 ml) was added and the mixture was refluxed for 30 min. Water (700 ml) was added and the soln was shaken with ether. The ether layer was discarded and the water layer was acidified with dil HCl saturated with NaCl and extracted with ether. From the ether extract upon vacuum distillation 42.5 g (77.8%) of **19** were obtained, b.p. 146° (19 mm) lit.[27] 141° (15 mm).

1,2,3,4-*Tetramethoxybenzene* (**20**). A mixture of phenol **19** (70 g, 0.38 mole), dimethyl sulphate (40 ml, 0.42 mole), K_2CO_3 (140 g, 1 mole) and acetone (500 ml) was refluxed for 22 hr. The solvent was distilled off and water (500 ml) was added to the residue. After several hr standing at room temp, the crystalline product was collected, washed with water and dried (74.7 g, m.p. 88–91°). Upon recrystallisation from MeOH 74.3 g (97.0%) of **20** were obtained, m.p. 91° (lit.[4] 89.5–90°).

2,3,4,5-*Tetramethoxybromobenzene* (**23**). Compound **20** (40.0 g, 0.20 mole) was dissolved in purified CH_2Cl_2 (200 ml) and Br_2 (32 g, 0.20 mole) in CH_2Cl_2 (20 ml) was added dropwise while the mixture was stirred at −10°. After the usual work-up, vacuum distillation afforded 51.2 g (92%) of **23**, b.p. 157/12 mm. The compound solidified in the refrigerator and was recrystallised from MeOH, m.p. 36–38°. NMR (CCl_4) δ 4.09 (9H,s, 3-, 4-, and 5-OCH_3), 4.14 (3H, s, 2-OCH_3), 6.95 (1H, s, 6-H). (Found: C, 43.60; H, 4.65; Br, 29.20. Calcd. for $C_{10}H_{13}O_4Br$, C, 43.50; H, 4.70; Br 29.00%).

2,3,4,5-*Tetramethoxybenzaldehyde* (**21**). To N-methyl-N-phenylformamide (36 g, 0.266 mole), freshly distilled $POCl_3$ (42 g, 0.274 mole) was added and the mixture was left at room temp for 30 min. Then **20** (40 g, 0.213 mole) was added. After standing for 72 hr at room temp, the same complex ($POCl_3$ (4.5 g) with N-methyl-N-phenylformamide (4.0 g)) was added and the mixture was left for another 72 hr at room temp. The reaction was completed by heating at 40° for 3 hr. After cooling to room temp it was poured into ice water (1 l). The crystalline product was collected, washed with water and dried *in vacuo* to yield 36.5 g. Recrystallisation from hexane afforded 36.1 g (80%) of **21**, m.p. 37–39°, b.p. 147°/5 mm, m.p. of 2,4-dinitrophenylhydrazone 194° (lit.[28] 194–195°).

1-*Methyl*-2,3,4,5-*tetramethoxybenzene* (**22**)

Method A. Compound **21** (16 g, 0.075 mole) in glacial AcOH (80 ml) containing 1 ml of conc HCl was hydrogenated over 10% Pd—C (1.0 g) at atmospheric pressure (the progress of hydrogenation was monitored by tlc). After 48 hr, the same catalyst (1 g) was added and the hydrogenation continued for another 48 hr. The next portion (0.5 g) of catalyst was added and the hydrogenation was continued for 24 hr. Then the catalyst was removed by filtration and the extractive (ether) work-up and vacuum distillation afforded 10.0 g (67%) of **22**, b.p. 128–130° (10 mm or 108°) 3 mm. NMR (CCl_4): δ 2.34 (3H, s, 1-CH_3), 3.95–4.04 (12H, m, 2-, 3-, 4- and 5-OCH_3), 6.50 (1H, s, 6-H). (Found: C, 62.25; H, 7.59. Calcd. for: $C_{11}H_{16}O_4$, C, 62.50; H, 7.55%).

Method B. A soln of **23** (14 g, 0.05 mole) was cooled in an ice-salt bath and while stirred, n-BuLi (0.06 mole) in Et_2O (50 ml) was added dropwise under N_2 and a white ppt formed. The stirring was continued for 30 min at low temp after the addition. Then methyl *p*-toluenesulphonate (11.0 g, 0.06 mole) in Et_2O (30 ml) was added dropwise at the same temp (an ice-salt bath). The mixture was then stirred for an hr at the low temp, for 10 hr at room temp and for 3 hr under reflux.Finally water was added and the layers separated. Vacuum distillation afforded 7.7 g (73%) of **22**. The product was contaminated by a small amount of **20**. Purification was accomplished by redissolving in hexane (20 ml), standing at 5° for several hours, filtration (**20** remains undissolved) and vacuum distillation.

2-*Methyl*-3,4,5,6-*tetramethoxybromobenzene* (**25**). To stirred **22** (10.6 g, 0.05 mole) in CH_2Cl_2 (50 ml), Br_2 (8.0 g, 0.05 mole) in CH_2Cl_2 (10 ml) was added dropwise at 3–5°. The mixture was successively washed with water, diluted NaOH, then water and dried over K_2CO_3. After vacuum distillation 12.0 g (83%) of **15** were obtained, b.p. 127°/5 mm or 155°/11 mm. NMR (CCl_4), δ 2.50 (3H, s, 2-CH_3), 4.00-4.13 (12H, m, 3-, 4-, 5-, and 6-OCH_3). (Found: C, 45.93: H, 5.09: Br, 26.91. Calcd. for: $C_{11}H_{15}O_4Br$, C, 45.40; H, 5.15; Br, 27.50%).

1-*Geranyl*-2-*methyl*-3,4,5,6-*tetramethoxybenzene* (**2**). To a stirred and ice cooled **25** (5.82 g, 0.20 mole) in Et_2O (30 ml) n-BuLi (0.023 mole) in Et_2O (20 ml) was added dropwise under N_2. During the addition a white ppt was formed. The stirring was continued for 30 min and CuBr (4.0 g, 0.014 mole) was added portionwise. The mixture became homogeneous while stirred for 3 hr. Then geranyl bromide (obtained from Aldrich Gold Labeled geraniol in accordance with lit.[29]) (4.77 g, 0.022 mole) in Et_2O (20 ml) was added dropwise. The mixture was stirred for 2 hr at 0° and for 4 hr at room temp. After decomposition with dil HCl the layers were separated. The ether layer was successively washed with water, satd $NaHCO_3$aq and again with water, and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography on alumina using benzene as eluent to yield 5.30 g (76%) of **2**. Colourless oil. NMR ($CDCl_3$) δ 1.85 and 1.90 (6H, s, $=C(CH_3)_2$); 2.05 (3H, s, $=C(CH_3)$—); 2.27 (4H, m, $—CH_2CH_2—$); 2.40 (3H, s, 2-CH_3); 3.65 (2H, d, J = 6 Hz, $—CH_2—$); 4.05 and 4.18 (12H, s, $—OCH_3$); 5.32 (1H, t, J = 6 Hz, $=CH—$). (Found: C, 72.31; H, 8.97. Calcd. for: $C_{21}H_{32}O_4$, C, 72.38; H, 9.25%).

1-*Geranyl*-2-*methyl*-4,5-*dimethoxybenzoquinone* (**4**) (*ubiquinone*-2). Compound **2** was oxidised as described in general procedures to give **4** as a yellow oil; IR (film) 1650 cm^{-1} ($\nu_{c=O}$), NMR ($CDCl_3$) δ 1.87 and 1.95 (6H, s, $=C(CH_3)_2$); 2.05 (3H, s, $=C(CH_3)$—); 2.32 (4H, m, $—CH_2CH_2—$); 2.45 (3H, s, 2-CH_3); 3.52 (2H, d, J = 6Hz, $—CH_2—$); 4.22 and 4.32 (6H, s, $—OCH_3$); 5.43 (1H, t, J = 6 Hz, $=CH—$). (Found: C, 71.52; H, 8.00, Calcd. for: $C_{19}H_{26}O_4$, C, 71.67; H, 8.23%).

1-*allyl*-2-*methyl*-3,4,5,6-*tetramethoxybenzene* (**1**). This compound was obtained by the method described for the preparation of **2**, using allyl bromide instead of geranyl bromide. The product was purified on alumina using benzene-cyclohexane (1:1) as eluent. The yield of 1 was

3.85 g (76%). It was a colourless oil; NMR ($CDCl_3$), δ 2.47 (3H, s, 2-CH_3); 3.70 (2H, d, J = 7 Hz, —CH_2—); 4.07, 4.10, 4.14, and 4.25 (12H, s, —OCH_3); 5.07–5.40 (2H, m, =CH_2); 6.00–6.47 (1H, m, —CH=). (Found: C, 66.47; H, 7.99. Calcd. for: $C_{14}H_{20}O_4$, C, 66.64; H, 7.99%).

1-*Allyl*-2-*methyl*-4,5-*dimethoxybenzoquinone* (**3**). Compound **1** was oxidised as described in general procedures to give **3** as an yellow oil, IR (film) 1650 cm^{-1} ($\nu_{C=O}$). NMR ($CDCl_3$), δ 2.27 (3H, s, 2-CH_3); 3.50 (2H, d, J = 6 Hz, —CH_2—); 4.25 (6H, s, —OCH_3); 5.10–5.45 (2H, m, =CH_2); 5.75–6.20 (1H, m, —CH=). (Found: C, 64.92; H, 6.12. Calcd. for: $C_{12}H_{14}O_4$, C, 64.85, H, 6.35.)

2-*Allyl*-3-*methyl*-1,4-*dimethoxynaphthalene* (**5**). This compound was prepared as described for **1** and **2** starting from 2-bromo-3-methyl-1,4-dimethoxynaphthalene[30] and allyl bromide. The lithium–bromide exchange was accomplished by C_6H_5Li in Et_2O or n-BuLi in hexane. The product was purified on alumina impregnated with $AgNO_3$ (10:1 by weight) using benzene-cyclohexane (1:1) as eluent, and by successive recrystallisation from MeOH. The yield of **5** was 62%. Colourless plates m.p. 46°, NMR ($CDCl_3$), δ 2.62 (3H, s, 3-CH_3); 3.85 (2H, d, J = 6 Hz, —CH_2—); 4.07 and 4.11 (6H, s, —OCH_3); 4.98–5.40 (2H, m, =CH_2); 6.00–6.50 (1H, m, =CH—); 7.76–7.82 (2H, m, 6-H and 7-H); 8.25–8.40 (2H, m, 5-H and 8-H). (Found: C, 79.15; H, 7.40. Calcd. for: $C_{16}H_{18}O_2$, C, 79.30; H, 7.48%).

2-*Allyl*-3-*methyl*-1,4-*naphthoquinone* (**8**). Compound **5** was oxidised as described to give crude **8**. It recrystallised from EtOH as yellow needles, m.p. 74-75°; IR (KBr) 1660 cm^{-1} ($\nu_{C=O}$), NMR ($CDCl_3$), δ 2.25 (3H, s, 3-CH_3); 3.71 (2H, d, J = 6 Hz, —CH_2—); 5.30–5.50 (2H, m, =CH_2); 5.90–6.32 (1H, m, —CH=); 7.98 (2H, dd, J = 4 Hz and 6 Hz, 6-H and 7-H); 8.37 (2H, dd, J = 4 Hz and 6 Hz, 5-H and 8-H). (Found: C, 80.31; H, 8.07. Calcd. for: $C_{14}H_{12}O_2$, 79.96; H, 8.20%).

2-*Prenyl*-3-*methyl*-1,4-*dimethoxynaphthalene* (**6**). This compound was obtained in 68% yield as described for **1**, **2** and **5**, starting from **32** and prenyl bromide. n-BuLi in Et_2O was used for the Li–Br exchange. The product was purified on silica gel using benzene–cyclohexane (1:1) as eluent. Colourless oil (lit.[10]). NMR ($CDCl_3$), δ 2.05 and 2.20 (6H, s, =$C(CH_3)_2$); 2.82 (3H, s, 2-CH_3); 3.87 (2H, d, J = 6 Hz, —CH_2—); 4.29 and 4.32 (6H, s, —OCH_3); 5.48 (1H, m, =CH—); 7.72 (2H, dd, J = 4 Hz and 6 Hz, 6-H and 7-H); 8.25-8.60 (2H, m, 5-H and 8-H).

2-*Prenyl*-3-*methyl*-1,4-*naphthoquinone* (**9**) (*Menaquinone*-1). Compound **6** was oxidised as described to give **9** as a yellow oil (lit.[10]). IR (film) 1658 cm^{-1} ($\nu_{C=O}$) NMR ($CDCl_3$), δ 2,05 and 2.18 (6H, s, =$C(CH_3)_2$); 2.55 (3H, s, —CH_3); 3.57 (2H, d, J = 6 Hz, —CH_2—); 5.35 (1H, m, =CH—); 7.97 (2H, dd, J = 4 Hz and 6 Hz, 6-H and 7H); 8.25–8.45 (2H, dd, 4 Hz and 6 Hz, 5-H and 8-H).

2-*Geranyl*-3-*methyl*-1,4-*dimethoxynaphthalene* (**7**). This compound was prepared as described for **2**. n-BuLi in Et_2O was used for the bromide exchange. The product was purified by column chromatography on silica gel impregnated with $AgNO_3$ (10:1 by weight), using benzene for elution. Starting from 2.81 g (0.01 mole) of 2-bromo-3-methyl-1,4-dimethoxynaphthalene and 2.17 g 0.01 mole of geranyl bromide, 2.63 g (78%) of pure **7** was obtained as a colourless oil (lit.[11]). NMR ($CDCl_3$) δ 1.95 and 2.05 (6H, s, =$C(CH_3)_2$); 2.20 (3H, s, =$C(CH_3)$—); 2.42 (4H, m, —CH_2—CH_2—); 2.75 (3H, s, 3-CH_3); 3.90 (2H, d, J = 6 Hz, —CH_2—); 4.28 (6H, s, —OCH_3); 5.42 (1H, m, —CH=); 7.72 (2H, d, J = 4 Hz and 6 Hz, 6-H and 7-H); 8.35 (2H, dd, J = 4 Hz and 6 Hz, 5-H and 7-H.

2-*Geranyl*-3-*methyl*-1, 4-*naphthoquine* (**10**) (*Menaquinone*-2). Compound **7** was oxidised as described to give **10** as a yellow oil; (lit.[11]) IR (film) 1657 cm^{-1} ($\nu_{C=O}$). NMR ($CDCl_3$), δ 1.97 and 2.05 (6H, s, =$C(CH_3)_2$); 2.18 (3H, s, =$C(CH_3)$—); 2.38 (4, m, —CH_2—CH_2—); 2.60 (3H, s, 3-CH_3); 3.75 (2H, d, J = 6 Hz, —CH_2—); 5.40 (1H, m, —CH=); 7.98 (2H, dd, J = 4 Hz and 6 Hz, 6-H and 7-H); 8.30–8.45 (2H, m, 5-H and 8-H).

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