[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

COMPOUNDS WITH POTENTIAL ACTIVITY AGAINST LETHAL RADIATIONS. V.[1] METHYL HOMOLOGS OF 1,5-DIHYDROXYNAPHTHALENE

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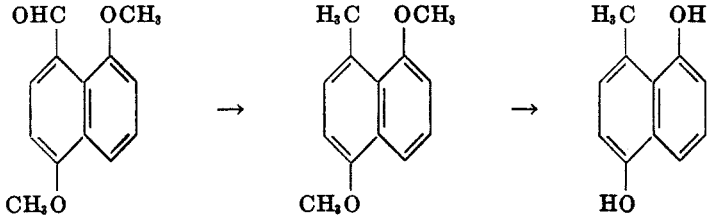
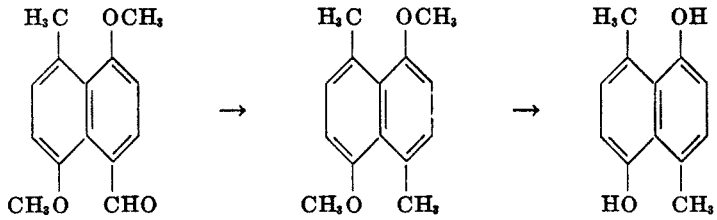
Derivatives of polyphenols and naphthols have been shown to possess protective properties against lethal radiations *in vivo* (1). *In vitro*, naphthols have been found to inhibit the x-ray depolymerization of polystyrolene (2), and autoxidation (3), both of which processes probably play an important role in the harmful effects of irradiation. These considerations led us to study derivatives of 1,5-dihydroxynaphthalene, itself an antioxidant (4). In particular, methyl homologs of 1,5-dihydroxynaphthalene have been synthesized for biological examination, as they would be more soluble in lipids than the parent compound.



I II III

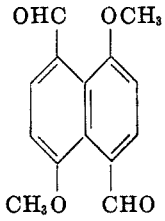
1,5-Dimethoxynaphthalene condensed readily with N-methylformanilide to give 4,8-dimethoxy-1-naphthaldehyde (I); Kishner-Wolff reduction of the latter by means of Huang-Minlon's technique (5) afforded 4,8-dimethoxy-1-methylnaphthalene (II), which was demethylated by pyridine hydrochloride to 4,8-dihydroxy-1-methylnaphthalene (III). This compound was highly autoxidizable, and its solutions underwent rapid alteration in the air. The higher homolog, 4,8-dihydroxy-1,5-dimethylnaphthalene (VI), which showed similar properties, was prepared by formylation of 4,8-dimethoxy-1-methylnaphthalene to 4,8-dimethoxy-1-methyl-5-naphthaldehyde (IV), reduction of the latter to 4,8-dimethoxy-1,5-dimethylnaphthalene (V), and subsequent pyridine hydrochloride demethylation.



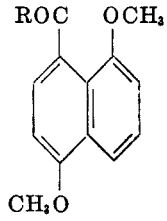
IV V VI

[1] Part IV, *Buu-Hoï and Lavit, J. Org. Chem.*, **20**, 823 (1955).

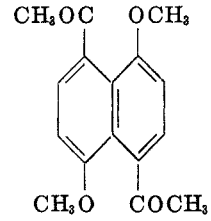
An alternative route to V, which was more direct but which gave unsatisfactory yields, was the diformylation of 1,5-dimethoxynaphthalene to 1,5-diformyl-4,8-dimethoxynaphthalene (VII), and reduction of the latter.



VII



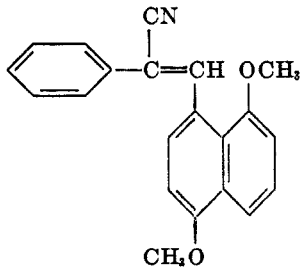
VIII: R = CH_3
IX: R = C_2H_5



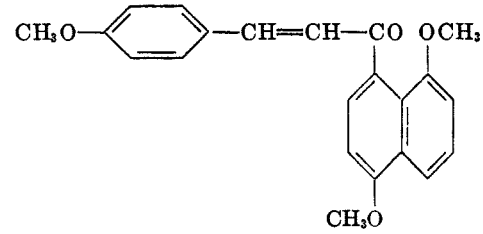
X

An attempt to synthesize ethyl and propyl homologs of 1,5-dihydroxynaphthalene failed, as 4,8-dimethoxy-1-acetonaphthone (VIII) and 4,8-dimethoxy-1-propionaphthone (IX) (readily prepared by a Friedel-Crafts reaction on 1,5-dimethoxynaphthalene) underwent total resinification under the conditions of the Huang-Minlon reduction. This was also the case with 1,5-diacetyl-4,8-dimethoxynaphthalene (X), obtained as a by-product in the Friedel-Crafts acetylation of 1,5-dimethoxynaphthalene. Equally unsuccessful was an attempt to demethylate ketones (VIII) and (IX) to the corresponding hydroxy compounds. Treatment with pyridine hydrochloride led to resinification, whereas heating with a mixture of hydrobromic and acetic acid resulted in the splitting of the ketones and recovery of 1,5-dimethoxynaphthalene. The easy hydrolytic fission of ketones derived from 1,5-dimethoxynaphthalene had previously been observed by Hill, Short, and Stromberg (6) during an attempt to reduce β-(4,8-dimethoxy-1-naphthoyl)propionic acid by the Clemmensen method. It is worth noting that mineral acid-catalyzed fission of the ketone group occurred prior to any splitting of the methyl ether groups present in the naphthalenes.

With regard to steric hindrance, it was interesting to observe that whereas the carbonyl group in the molecule of 4,8-dimethoxy-1-naphthaldehyde appeared normally reactive, as witnessed the easy formation of α-phenyl-β-(4,8-dimethoxy-1-naphthyl)acrylonitrile (XI) with benzyl cyanide, the carbonyl group in the molecule of 4,8-dimethoxy-1-acetonaphthone was sterically hindered, and failed to undergo a Pfitzinger reaction with isatin. On the other hand,



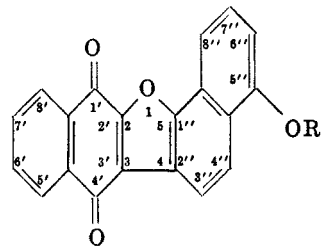
XI



XII

the methyl group in the molecule of the latter ketone, being more remote from the naphthalene nucleus, is consequently less hindred, and readily gave the chalkone (XII) with anisaldehyde.

1,5-Dihydroxynaphthalene was found to react with 2,3-dichloro-1,4-naphthoquinone in pyridine (7) to give 5″-hydroxydinaphtho[2′,3′-2,3] [1″,2″-5,4]furan-1′,4′-quinone[2] (XIII). This compound was also prepared by pyridine hydrochloride demethylation of 5″-methoxydinaphtho[2′,3′-2,3]



XIII: R = H
XIV: R = CH_3

[1″,2″-5,4-]furan-1′,4′-quinone (XIV), obtained by condensation of 5-methoxy-1-naphthol with 2,3-dichloro-1,4-naphthoquinone.

EXPERIMENTAL

4,8-Dimethoxy-1-naphthaldehyde (I). 1,5-Dimethoxynaphthalene was prepared by methylation of 1,5-dihydroxynaphthalene with dimethyl sulfate and aqueous potassium hydroxide, and was purified by distillation *in vacuo* (b.p. 179°/13 mm.). A mixture of 30 g. of 1,5-dimethoxynaphthalene, 28 g. (1.3 moles) of N-methylformanilide, and 28 g. of phosphorus oxychloride in 30 ml. of dry toluene was heated on a water-bath for six hours (vigorous reaction at the beginning). The reaction mixture was shaken with aqueous sodium hydroxide for 30 minutes, the aldehyde taken up in benzene, and the benzene solution washed with dilute hydrochloric acid then with water, and dried over sodium sulfate. The aldehyde obtained on evaporation of the solvent was purified by distillation *in vacuo*. Yield: 28 g. of a product boiling at 226–227°/12 mm., crystallizing from ethanol in colorless prisms, m.p. 126°.

Anal. Calc'd for $C_{13}H_{12}O_3$: C, 72.2; H, 5.6.
Found: C, 72.5; H, 5.6.

The *thiosemicarbazone* crystallized from acetic acid in yellowish prisms, m.p. 265° (decomp. above 230° on prolonged heating).

Anal. Calc'd for $C_{14}H_{15}N_3O_2S$: C, 58.1; H, 5.2.
Found: C, 58.4; H, 5.3.

The *4-keto-Δ^2-thiazolin-2-ylhydrazone*, prepared by refluxing equimolecular amounts of the foregoing thiosemicarbazone and chloroacetic acid with sodium acetate in acetic acid solution, crystallized from ethanol in pale yellow needles, m.p. 248°.

Anal. Calc'd for $C_{16}H_{15}N_3O_3S$: C, 58.4; H, 4.6.
Found: C, 58.2; H, 4.4.

α-Phenyl-β-(4,8-dimethoxy-1-naphthyl)acrylonitrile (XI). To a warm solution of 2 g. of aldehyde I and 1.3 g. of benzyl cyanide in 70 ml. of ethanol, 1 ml. of a 20% aqueous solution of sodium hydroxide was added with stirring. The solid precipitate crystallized from ethanol in yellow needles, m.p. 105–106°.

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[2] Chemical Abstracts name is 11-Hydroxydinaphtho[2,3,1′,2′]furan-1,6-dione.

Anal. Calc'd for $C_{21}H_{17}NO_2$: C, 80.0; H, 5.4.
Found: C, 79.7; H, 5.4.

4,8-Dimethoxy-1-methylnaphthalene (II). A mixture of 10 g. of aldehyde I, 4 g. of 95% hydrazine hydrate, and 175 ml. of diethylene glycol was heated until the barely soluble aldehyde was converted to the easily soluble hydrazone. The solution was refluxed with 4 g. of potassium hydroxide for 45 minutes, water was added on cooling, and the precipitate obtained was collected, washed with dilute hydrochloric acid then with water, dried, and distilled *in vacuo*. Yield, 7.5 g. of a product boiling at 187–188°/16 mm., crystallizing from ethanol in shiny colorless leaflets, m.p. 105°.

Anal. Calc'd for $C_{13}H_{14}O_2$: C, 77.2; H, 6.9.
Found: C, 77.2; H, 7.0.

The corresponding *picrate* crystallized from ethanol in brown-violet needles, m.p. 160°.

4,8-Dihydroxy-1-methylnaphthalene (III). A mixture of 2 g. of ether II and 12 g. of redistilled pyridine hydrochloride was refluxed for 15 minutes. After cooling, water was added, and the reaction product was taken up in ether. The ethereal solution was dried over sodium sulfate, and the solid obtained on evaporation of solvent was quickly crystallized from toluene, to give 1 g. of fine, colorless, sublimable needles, m.p. 190°. The solutions in toluene or ethanol darkened rapidly in the air, and a greenish-yellow product was obtained on evaporation.

Anal. Calc'd for $C_{11}H_{10}O_2$: C, 75.9; H, 5.7.
Found: C, 75.6; H, 5.6.

4,8-Dimethoxy-1-methyl-5-naphthaldehyde (IV). A mixture of 16.5 g. of 4,8-dimethoxy-1-methylnaphthalene, 14.5 g. (1.3 moles) of *N*-methylformanilide, 14.5 g. of phosphorus oxychloride, and 15 ml. of dry toluene was treated as for I. Yield, 16 g. of an aldehyde, b.p. 236–237°/13 mm., crystallizing from ethanol in yellowish needles, m.p. 152°.

Anal. Calc'd for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1.
Found: C, 72.9; H, 6.3.

The *thiosemicarbazone* crystallized from acetic acid in pale yellow prisms, m.p. 278° (decomp. above 250° on prolonged heating).

Anal. Calc'd for $C_{15}H_{17}N_3O_2S$: C, 59.4; H, 5.6.
Found: C, 59.6; H, 5.8.

The *4-keto-Δ^2-thiazolin-2-ylhydrazone* crystallized from ethanol in pale yellow needles, m.p. 280°.

Anal. Calc'd for $C_{17}H_{17}N_3O_3S$: C, 59.5; H, 5.0.
Found: C, 59.1; H, 5.1.

4,8-Dimethoxy-1,5-dimethylnaphthalene (V). The foregoing aldehyde (IV) (10 g.) was reduced with 4 g. of hydrazine hydrate and 4 g. of potassium hydroxide in diethylene glycol as for the lower homolog. Yield, 7.5 g. of a product b.p. 184–185°/11 mm., crystallizing from ethanol in shiny colorless needles, m.p. 126°.

Anal. Calc'd for $C_{14}H_{16}O_2$: C, 77.8; H, 7.4.
Found: C, 77.7; H, 7.5.

The corresponding *picrate* crystallized from ethanol in dark brown silky needles, m.p. 175°.

4,8-Dihydroxy-1,5-dimethylnaphthalene (VI). A mixture of 3.5 g. of the foregoing methyl ether and 45 g. of pyridine hydrochloride was refluxed for ten minutes. Water was added on cooling, and the precipitate was collected, washed with water, dried in a vacuum, and purified by rapid recrystallization from toluene, and sublimation. Yield, 2 g. of shiny colorless needles, m.p. 218°.

Anal. Calc'd for $C_{12}H_{12}O_2$: C, 76.6; H, 6.4.
Found: C, 76.8; H, 6.1.

1,5-Diformyl-4,8-dimethoxynaphthalene (VII). A mixture of 20 g. of 1,5-dimethoxynaphthalene, 37 g. (2.6 moles) of N-methylformanilide, 37 g. of phosphorus oxychloride, and 20 ml. of dry toluene was heated at 100° for 6 hours. After usual treatment with aqueous sodium acetate, the aldehyde I (yield: 18 g.) was taken up in benzene, and the solid that

remained was collected, washed with water, and recrystallized from acetic acid. Yield, 1 g. of yellow sublimable needles, m.p. 282°.

Anal. Calc'd for $C_{14}H_{12}O_4$: C, 68.9; H, 4.9.
Found: C, 68.6; H, 5.1.

Kishner-Wolff reduction (Huang-Minlon's technique) of this dialdehyde gave 4,8-dimethoxy-1,5-dimethylnaphthalene, m.p. 126°.

Acetylation of 1,5-dimethoxynaphthalene. 1,5-Dimethoxynaphthalene (30 g.) was dissolved in 400 ml. of warm nitrobenzene. The solution was quickly cooled, and the resulting suspension was treated portionwise with 14 g. of acetyl chloride, and then with 24 g. of aluminum chloride. After keeping overnight at room temperature, the mixture was decomposed with ice, and the nitrobenzene was steam-distilled. The reaction product was taken up in benzene, the benzene solution washed first with a 5% aqueous solution of sodium hydroxide, then with water, dried over sodium sulfate, the solvent evaporated, and the residue vacuum-fractionated. (*a*) *4,8-Dimethoxy-1-acetonaphthone* (VIII) (30 g.), b.p. 217–218°/12 mm., crystallized from ethanol in colorless needles, m.p. 96°, giving a yellow halochromy with sulfuric acid.

Anal. Calc'd for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1.
Found: C, 73.1; H, 6.3.

(*b*) The higher-boiling portion (240–250°/12 mm.) was recrystallized from ethanol, to give 1 g. of *1,5-diacetyl-4,8-dimethoxynaphthalene* (X), colorless needles, m.p. 197°.

Anal. Calc'd for $C_{16}H_{16}O_4$: C, 70.6; H, 5.9.
Found: C, 70.8; H, 6.3.

Both ketones gave black resins on treatment with hydrazine hydrate and potassium hydroxide in diethylene glycol. Ketone VIII was recovered unchanged after 6 days' refluxing of its solution in ethanol with isatin and potassium hydroxide.

1-p-Methoxycinnamoyl-4,8-dimethoxynaphthalene (XII). A solution of 1 g. of ketone VIII and 0.6 g. of anisaldehyde in warm ethanol was shaken with 1 ml. of a 20% aqueous solution of sodium hydroxide. The precipitate which formed after a few hours crystallized from ethanol to give yellowish needles, m.p. 112°; the melted compound resolidified at around 90°, and melted once more at 124°. The solution in sulfuric acid was blood red.

Anal. Calc'd for $C_{22}H_{20}O_4$: C, 75.9; H, 5.7.
Found: C, 75.8; H, 5.7.

4,8-Dimethoxy-1-propionaphthone (IX). A mixture of 30 g. of 1,5-dimethoxynaphthalene, 16 g. of acetyl chloride, and 300 ml. of nitrobenzene was treated with 24 g. of aluminum chloride as for ketone VIII. Yield, 26 g. of a *ketone*, b.p. 224–225°/12 mm., crystallizing from ethanol as shiny colorless needles, m.p. 83°.

Anal. Calc'd for $C_{15}H_{16}O_3$: C, 73.8; H, 6.6.
Found: C, 73.5; H, 6.8.

This ketone was also completely resinified on treatment with hydrazine hydrate and potassium hydroxide in diethylene glycol.

5″-Hydroxydinaphtho[2′,3′-2,3][1″,2″-5,4]furan-1′,4′-quinone[2] (XIII). A solution of 1.5 g. of 1,5-dihydroxynaphthalene, 2.1 g. of 2,3-dichloro-1,4-naphthoquinone, and 15 ml. of anhydrous pyridine was refluxed for 5 hours. After cooling, methanol was added, and the precipitate which formed was collected, washed with methanol, dried, and recrystallized from nitrobenzene. Yield, 2.5 g. of brown, sublimable needles, m.p. 315°, giving a characteristic blue coloration with sulfuric acid or aqueous sodium hydroxide.

Anal. Calc'd for $C_{20}H_{10}O_4$: C, 76.4; H, 3.2.
Found: C, 76.1; H, 3.3.

5″-Methoxydinaphtho[2′,3′-2,3][1″,2″-5,4-]furan-1′,4′-quinone (XIV). A solution of 1.5 g. of 5-methoxy-1-naphthol (8), 2 g. of 2,3-dichloro-1,4-dichloronaphthoquinone, and 15 ml. of pyridine was treated as above. Yield, 2.6 g. The reaction product crystallized from nitrobenzene in shiny orange needles, m.p. 305°, giving a blue coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{12}O_4$: C, 76.8; H, 3.7.
Found: C, 76.7; H, 3.8.

SUMMARY

1. Two homologs of 1,5-dihydroxynaphthalene have been synthesized as potential antioxidants.

2. A number of new derivatives of 1,5-dihydroxy- and 1,5-dimethoxynaphthalene have been prepared, and their chemical properties have been investigated.

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