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

# Compounds with Potential Activity against Lethal Radiations. VII. Methyl and Ethyl Homologs of 1,7-Dihydroxynaphthalene

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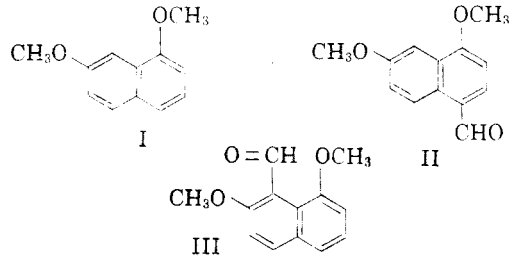
1,7-Dimethoxynaphthalene has been shown to undergo both formylation with dimethylformamide, and Friedel-Crafts acetylation, at position 4. Several methyl and ethyl homologs of 1,7-dihydroxynaphthalene have been synthesized for biological testing as potential agents against lethal radiation, and have shown marked antioxidant properties.

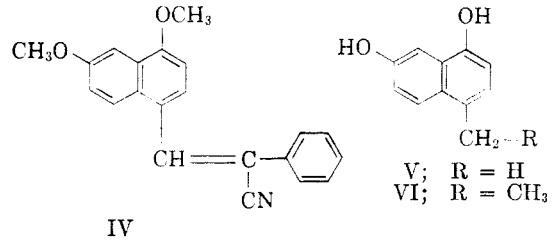
A three-step method was recently proposed for the synthesis of methyl homologs of 1,5-, 2,3-, 2,6-, and 2,7-dihydroxynaphthalene,[1] based on formylation of the corresponding dimethyl ether with dimethylformamide, reduction of the resulting aldehyde with hydrazine hydrate and potassium hydroxide, and demethylation of the reduction product with pyridine hydrochloride. This procedure has now been applied to the unsymmetrical 1,7-dihydroxynaphthalene, for the preparation of homologs required for biological studies on chemical protection against lethal radiation.

In the formylation of 1,7-dimethoxynaphthalene (I), the two positions expected to react are position 4 and position 8, position 4 being theoretically preferred in view of the greater reactivity of 1-methoxynaphthalene in formylation reactions as compared with 2-methoxynaphthalene. In fact, two isomeric aldehydes were obtained, one in good yield, and the other in far smaller quantity. The first isomer must have been 4,6-dimethoxy-1-naphthaldehyde (II) rather than the isomeric aldehyde III, as its condensation product (IV) with benzyl cyanide gave no coumarin derivative on demethylation with pyridine hydrochloride; a positive reaction would have been proof that the aldehyde group occupied a position *ortho* to a methoxy radical.[1,2] The lower-melting isomeric aldehyde was probably 2,8-dimethoxy-1-naphthaldehyde (III).



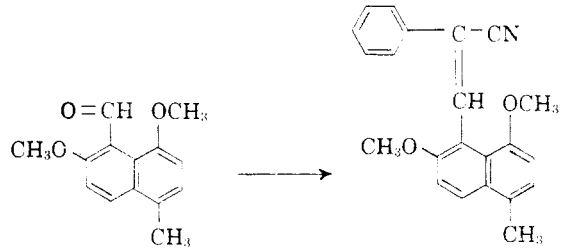
I II III

The formylation of 1,7-dimethoxynaphthalene thus recalls the Gattermann reaction with 1,7-dihydroxynaphthalene, which was found by Morgan and Vining to give a mixture of 4,6-dihydroxy-1-naphthaldehyde and some 2,8-dihydroxy-1-naphthaldehyde.[3]



IV V; R = H VI; R = $CH_3$

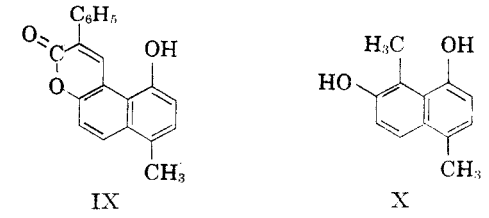
Kishner-Wolff reduction of aldehyde II readily afforded 4,6-dimethoxy-1-methylnaphthalene, which was demethylated to 4,6-dihydroxy-1-methylnaphthalene (V). Furthermore, 4,6-dimethoxy-1-methylnaphthalene readily underwent formylation to give a single aldehyde, probably 2,8-dimethoxy-5-methyl-1-naphthaldehyde (VII); the presence of a methoxy group in the position *ortho* to the aldehyde radical was shown by the fact that the acrylonitrile (VIII) obtained on condensation with benzyl cyanide was converted to a coumarin,



VII VIII

probably IX, on demethylation with pyridine hydrochloride.

Reduction of aldehyde VII gave 1,7-dimethoxy-4,8-dimethylnaphthalene, which on treatment with



IX X

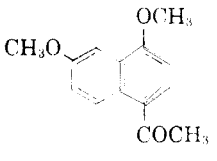
(1) Buu-Hoï and Lavit, *J. Org. Chem.*, **21**, 21 (1955); *J. Chem. Soc.*, 2776 (1953); 1743 (1956).

(2) Buu-Hoï and Eckert, *J. Org. Chem.*, **19**, 1391 (1954); Buu-Hoï, Eckert, and Royer, *J. Org. Chem.*, **19**, 1548) (1954); Buu-Hoï, Hoan, and Khenissi, *J. Chem. Soc.*, 2307 (1951).

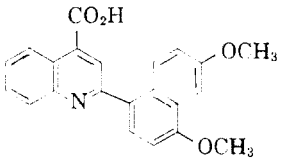
(3) Morgan and Vining, *J. Chem. Soc.*, **119**, 1707 (1921).

pyridine hydrochloride yielded 1,7-dihydroxy-4,8-dimethylnaphthalene (X).

Friedel-Crafts acetylation of 1,7-dimethoxynaphthalene gave a single ketone, which must have been 4,6-dimethoxy-1-acetonaphthone (XI), as a Pfitzinger reaction with isatin gave a cinchonic acid identical with that obtained from 4,6-dimethoxy-1-naphthaldehyde, aniline, and pyruvic acid by means of a Doebner reaction; this acid was therefore 2-(4,6-dimethoxy-1-naphthyl)cinchoninic acid (XII). Kishner-Wolff reduction of ketone XI led to 4,6-dimethoxy-1-ethylnaphthalene, which in turn afforded 4,6-dihydroxy-1-ethylnaphthalene (VI).




XI




XII

The dihydroxynaphthalenes reported herein showed good antioxidant properties, and are being tested in this Institute by Dr. F. Duplan for activity against lethal radiations.

## EXPERIMENTAL

*1,7-Dimethoxynaphthalene* (I). To a freshly prepared solution of 100 g. of 1,7-dihydroxynaphthalene in a 10% aqueous solution of 77 g. of potassium hydroxide, 181 g. of dimethyl sulfate was added portionwise with stirring. The flask containing the mixture then was heated for 15 minutes on a water-bath, and a further 20 g. of potassium hydroxide was added, followed by the equivalent amount of dimethyl sulfate. After cooling, and basification with more potassium hydroxide, the reaction product was taken up in ether, the ethereal solution dried over sodium sulfate, the solvent removed, and the residue vacuum-fractionated. Yield, 73 g. of a pale yellow oil, b.p. 170°/20 mm., $n_D^{25}$ 1.6212, with a strong neroline odor.

*Anal.* Calc'd for $C_{12}H_{12}O_2$: C, 76.6; H, 6.4. Found: C, 76.5; H, 6.4.

The *picrate* crystallized from ethanol in shiny red prisms, m.p. 133°.

*Anal.* Calc'd for $C_{18}H_{15}N_3O_9$: N, 10.1. Found: N, 10.4.

*Formylation of 1,7-dimethoxynaphthalene.* A mixture of 50 g. of 1,7-dimethoxynaphthalene, 25 g. of dimethylformamide, and 47 g. of phosphorus oxychloride was gently refluxed on the water-bath for 5 hours. A concentrated aqueous solution of sodium acetate then was added, and the mixture was refluxed for 30 minutes; after cooling, the reaction product was taken up in benzene, and the benzene solution was washed first with dilute hydrochloric acid, then with water, and dried over sodium sulfate. After evaporation of the solvent, the residue was vacuum-distilled, giving 45 g. of a product boiling at 242–244°/23 mm. Fractional crystallization from ethanol of 35 g. of this aldehyde mixture afforded 32 g. of *4,6-dimethoxy-1-naphthaldehyde* (II) as shiny colorless needles, m.p. 104°, giving an orange-red coloration in pure sulfuric acid.

*Anal.* Calc'd for $C_{13}H_{12}O_3$: C, 72.2; H, 5.6. Found: C, 72.1; H, 5.8.

The *thiosemicarbazone* of this aldehyde crystallized from ethanol in pale yellow prisms, m.p. 224°.

*Anal.* Calc'd for $C_{14}H_{15}N_3O_2S$: C, 58.1; H, 5.2. Found: C, 57.8; H, 5.1.

The mother liquors from the crystallization of aldehyde II yielded after concentration and several days' standing in the refrigerator, 1 g. of a second aldehyde, probably *2,8-dimethoxy-1-naphthaldehyde*, which crystallized from methanol in shiny colorless prisms, m.p. 90°; these likewise gave an orange-red coloration with sulfuric acid.

*Anal.* Calc'd for $C_{13}H_{12}O_3$: C, 72.2; H, 5.6. Found: C, 72.0; H, 5.9.

It should be noted that in the Gattermann reaction with 1,7-dihydroxynaphthalene, Morgan and Vining[3] obtained a 44% yield of 4,6-dihydroxy-1-naphthaldehyde and 38% of 2,8-dihydroxy-1-naphthaldehyde.

*1-Phenyl-2-(4,6-dimethoxy-1-naphthyl)acrylonitrile* (IV). To a warm (50–60°) solution of 2 g. of aldehyde II and 1.1 g. of benzyl cyanide in 30 ml. of ethanol, two drops of a 30% aqueous solution of sodium hydroxide was added with shaking. After 15 minutes, the precipitate which formed on dilution with water was collected, washed with water, and crystallized from ethanol. Yield, 2 g. of pale yellow needles, m.p. 104°.

*Anal.* Calc'd for $C_{21}H_{17}NO_2$: C, 80.0; H, 5.4. Found: C, 80.1; H, 5.7.

This compound yielded no coumarin on heating with pyridine hydrochloride and subsequent hydrolysis.[4]

*4,6-Dimethoxy-1-methylnaphthalene.* A mixture of 30 g. of 4,6-dimethoxy-1-naphthaldehyde, 12 g. of 95% hydrazine hydrate, and 150 ml. of diethylene glycol was heated until dissolution, and 12 g. of potassium hydroxide then was added. The mixture was boiled with removal of water until evolution of nitrogen had ceased (20 minutes). After cooling, water was added, the reduction product was taken up in benzene, and the benzene solution was washed with dilute hydrochloric acid, then with water, and dried over sodium sulfate. Vacuum-distillation of the residue from evaporation of the solvent gave 26 g. of a product boiling at 190–191°/20 mm., which crystallized from ethanol in shiny colorless leaflets, m.p. 56°.

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

This compound gave a *picrate* which crystallized from ethanol in red needles, m.p. 138°.

*4,6-Dihydroxy-1-methylnaphthalene* (V). The foregoing ether (3 g.) was refluxed for 10 minutes with 18 g. of redistilled pyridine hydrochloride, and after cooling, water was added and the reaction product was taken up in ether. The solid residue obtained after evaporation of the solvent crystallized from benzene, giving 1.8 g. of colorless, sublimable needles, m.p. 162°, soluble in aqueous solutions of alkalis.

*Anal.* Calc'd for $C_{11}H_{10}O_2$: C, 75.8; H, 5.8. Found: C, 75.6; H, 5.6.

This compound, added in 0.1% concentration to linseed oil, showed marked antagonistic properties against the formation of fatty peroxides.

*2,8-Dimethoxy-5-methyl-1-naphthaldehyde* (VII). A mixture of 20 g. of 4,6-dimethoxy-1-methylnaphthalene, 9.5 g. of dimethylformamide, 17 g. of phosphorus oxychloride, and 20 ml. of toluene was heated for 6 hours on the water-bath, and the reaction mixture subsequently was worked up in the usual way. Yield, 16 g. of a single *aldehyde*, b.p. 242–243°/24 mm., crystallizing from ethanol in pale yellow needles, m.p. 102°.

*Anal.* Calc'd for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1. Found: C, 73.2; H, 6.2.

The corresponding *thiosemicarbazone* crystallized from ethanol in pale yellow needles, m.p. 239°.

*Anal.* Calc'd for $C_{15}H_{17}N_3O_2S$: C, 59.4; H, 5.6. Found: C, 59.1; H, 5.5.

*1-Phenyl-2-(2,8-dimethoxy-5-methyl-1-naphthyl)acrylonitrile* (VIII). A warm solution of 2 g. of aldehyde VII and 1 g. of benzyl cyanide in 30 ml. of ethanol was treated with aqueous sodium hydroxide as for compound IV, to yield

(4) Baker and Howes, *J. Chem. Soc.*, 119 (1953).

2 g. of an *acrylonitrile*, which crystallized from ethanol in pale yellow needles, m.p. 164°.

*Anal.* Calc'd for $C_{22}H_{19}NO_2$: C, 80.2; H, 5.8. Found: C, 80.0; H, 6.0.

A mixture of 0.5 g. of this acrylonitrile and 6 g. of pyridine hydrochloride was refluxed for 10 minutes, and water was added on cooling. The precipitate formed was collected and washed with water. This compound, probably *1'-hydroxy-4'-methyl-3-phenyl-5,6-benzocoumarin* (IX), crystallized from acetic acid in greenish-yellow prisms, m.p. 316°; its solutions in ethanol or acetic acid showed the strong green fluorescence characteristic of hydroxycoumarin derivatives.

*1,7-Dimethoxy-4,8-dimethylnaphthalene.* A solution of 9 g. of 2,8-dimethoxy-5-methyl-1-naphthaldehyde and 4 g. of hydrazine hydrate in 75 ml. of diethylene glycol was treated with 4 g. of potassium hydroxide in the usual way. Yield, 6 g. of a product boiling at 205–206°/23 mm., which crystallized from ethanol in silky colorless needles, m.p. 101°.

*Anal.* Calc'd for $C_{14}H_{16}O_2$: C, 77.8; H, 7.4. Found: C, 77.9; H, 7.4.

This compound gave a *picrate* which crystallized from ethanol in brown-red needles, m.p. 146°.

*1,7-Dihydroxy-4,8-dimethylnaphthalene* (X). Demethylation of 3 g. of the foregoing ether with 18 g. of pyridine hydrochloride as for the lower homolog (V), afforded 1.8 g. of a *dihydroxy compound*, crystallizing from benzene in gray-tinged prisms, m.p. 169°. This substance was readily soluble in aqueous alkalis, with a yellow coloration; it was highly autoxidizable in solution, and also showed strong inhibitory effects in the formation of peroxides in fats.

*Anal.* Calc'd for $C_{12}H_{12}O_2$: C, 76.6; H, 6.4. Found: C, 76.3; H, 6.2.

*4,6-Dimethoxy-1-acetonaphthone* (XI). To an ice-cooled solution of 20 g. of 1,7-dimethoxynaphthalene and 9.2 g. of acetyl chloride in 125 ml. of nitrobenzene, 16 g. of aluminum chloride was added in small portions with vigorous stirring. The dark green reaction mixture was left overnight at room temperature, then poured on ice; the nitrobenzene was removed by steam-distillation, and the reaction product was taken up in benzene. The benzene solution, washed with a dilute aqueous solution of sodium hydroxide, and then with water, was dried over sodium sulfate; the residue from evaporation of the solvent yielded on vacuum-distillation 22 g. of a ketone boiling at 238–239°/20 mm., which crystallized from ethanol in colorless needles, m.p. 88°. The solution in pure sulfuric acid was orange-red.

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

*2-(4,6-Dimethoxy-1-naphthyl)cinchoninic acid* (XII). A solution of 3 g. of the foregoing ketone, 2.1 g. of isatin, and 2.2 g. of potassium hydroxide in 50 ml. of ethanol was gently refluxed for 12 hours; after dilution with water, removal of the neutral impurities by ether-extraction, and acidification of the aqueous layer with acetic acid, a precipitate was obtained in 75% yield. This *cinchoninic acid* crystallized from ethanol in pale yellow prisms, m.p. 259–260°. The compound showed no depression in melting point when mixed with the reaction product from 4,6-dimethoxy-1-naphthaldehyde, aniline, and pyruvic acid.[5] 1-Acetonaphthones bearing a methoxy group in position 8 fail to give Pfitzinger reactions, on account of steric hindrance.[1]

*Anal.* Calc'd for $C_{22}H_{17}NO_4$: C, 73.5; H, 4.8. Found: C, 73.2; H, 4.6.

Thermal decarboxylation of this cinchoninic acid gave *2-(4,6-dimethoxy-1-naphthyl)quinoline*, characterized by its *picrate*, which crystallized from benzene in deep orange-yellow prisms, m.p. 218°.

*Anal.* Calc'd for $C_{27}H_{20}N_4O_9$: N, 10.3. Found: N, 10.0.

*4,6-Dimethoxy-1-ethylnaphthalene.* Reduction of 18 g. of ketone XI with 7 g. of hydrazine hydrate and 7 g. of potassium hydroxide in 150 ml. of diethylene glycol afforded 8.5 g. of 4,6-dimethoxy-1-ethylnaphthalene as a pale yellow oil, b.p. 202–203°/25 mm., $n_D^{24}$ 1.6083, with a strong neroline odor.

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

The corresponding *picrate* crystallized from ethanol in silky red needles, m.p. 115°.

*4,6-Dihydroxy-1-ethylnaphthalene* (VI). This compound crystallized from benzene in microscopic colorless needles, m.p. 158°, showing marked inhibitory activity against peroxide formation in fats.[6]

*Anal.* Calc'd for $C_{12}H_{12}O_2$: C, 76.6; H, 6.4. Found: C, 76.4; H, 6.5.

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(5) Doebner, *Ann.*, **242**, 280 (1887).

(6) *Cf.* Banks, *J. Soc. Chem. Ind. (Trans.)*, **63**, 8 (1944); Lea, *J. Soc. Chem. Ind. (Trans.)*, **63**, 55, 107 (1954).