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

Compounds with Potential Activity against Lethal Radiations. VI.[1] Homologs of 2,3-Dihydroxynaphthalene

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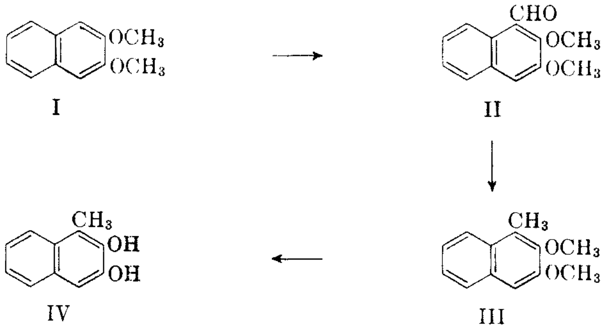
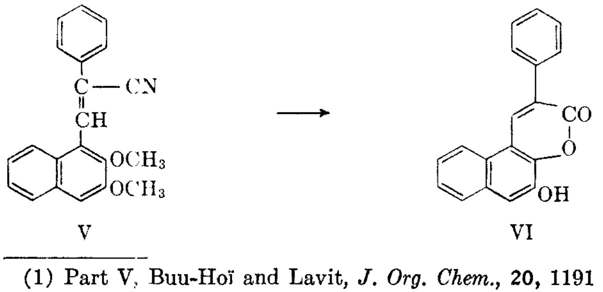
Several homologs of 2,3-dihydroxynaphthalene have been synthesized for biological testing as potential antagonists of lethal radiations. In the course of this work, the chemistry of 2,3-dimethoxynaphthalene has been investigated.

The protective effect of certain organic compounds against lethal radiations has sometimes been related to their ability to form chelate derivatives with metals such as copper.[2] This possibility suggested the preparation and testing of derivatives of *o*-dihydroxynaphthalenes which easily form Werner complexes with metals. 2,3-Dihydroxynaphthalene is particularly efficient in this respect,[3] and some of its homologs have now been synthesized, the alkyl groups being introduced with a view to enhancing their solubility in lipids.

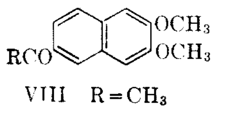
1-Methyl-2,3-dihydroxynaphthalene (IV) was prepared by the following sequence: reaction of 2,3-dimethoxynaphthalene (I) with dimethylformamide in the presence of phosphorus oxychloride, to give 2,3-dimethoxy-1-naphthaldehyde (II), Kishner-Wolff reduction of this aldehyde to 2,3-dimethoxy-1-methylnaphthalene (III), and subsequent demethylation with pyridine hydrochloride. The constitution of aldehyde (II) was determined by alkali-catalyzed condensation with benzyl cyanide to 1-phenyl-2-(2,3-dimethoxy-1-naphthyl)acrylonitrile (V), which was converted by demethylation to 8-hydroxy-3-phenyl-5,6-benzocoumarin (VI).

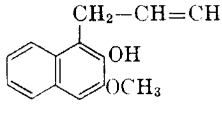

I II III IV


V VI

This cyclization proves that the formyl group enters the molecule of 2,3-dimethoxynaphthalene at the *ortho* position.[4] The high degree of reactivity of this position was further indicated by the ease with which the allyl ether of 2-hydroxy-3-methoxynaphthalene underwent the Claisen rearrangement to 1-allyl-2-hydroxy-3-methoxynaphthalene (VII); indeed, in this experiment the allyl ether could not be isolated.

Friedel-Crafts acetylation and propionylation of 2,3-dimethoxynaphthalene in nitrobenzene medium afforded 6-acetyl- (VIII) and 6-propionyl-2,3-dimethoxynaphthalene (IX), from which 6-ethyl- (X) and 6-propyl-2,3-dihydroxynaphthalene (XI) were obtained by Kishner-Wolff reduction and subsequent demethylation. In these experiments, the position entered by the acyl group was not rigidly proven, but was suggested by the analogous behavior of 2-methoxynaphthalene,[5] and supported by the high melting points of compounds (X) and (XI), reminiscent of that of their well-known lower homolog phyllomerol (6-methyl-2,3-dihydroxynaphthalene);[6] the melting points of their dimethyl ethers likewise lie within the same range as does that of phyllomerol dimethyl ether. Like 2,3-dihydroxynaphthalene itself, the 1-methyl, 6-ethyl, and 6-propyl homologs easily form complexes with metal salts, and give a characteristic deep blue coloration with a solution of ferric chloride in water or ethanol. They are fairly stable to air and light, unlike the homologs of 1,5-dihydroxynaphthalene which are highly oxidizable. Research is now being done in order to clear up the remaining uncertainty about the structure assigned to ketones VIII and IX.


VIII R = CH_3
IX R = CH_2CH_3


VII

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(1) Part V, Buu-Hoï and Lavit, *J. Org. Chem.*, **20**, 1191 (1955).

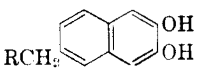
(2) Bacq, Hervé, and Fischer, *Bull. Acad. Roy. Med. Belg.*, **18**, 226 (1953).

(3) Friedländer and von Zakrzewski, *Ber.*, **27**, 761 (1894); Weinland and Seuffert, *Arch. Pharm.*, **266**, 455 (1928).

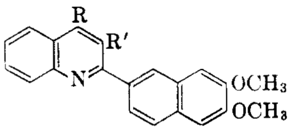
(4) See Buu-Hoï and Eckert, *J. Org. Chem.*, **19**, 1391 (1954); Buu-Hoï, Eckert, and Royer, *J. Org. Chem.*, **19**, 1548 (1954).

(5) Haworth and Sheldrick, *J. Chem. Soc.*, 864 (1934).

(6) Borsche and Niemann, *Ber.*, **53**, 4080 (1932); *Ann.*, **499**, 59 (1932); Robertson and Waters, *J. Chem. Soc.*, 83 (1933).

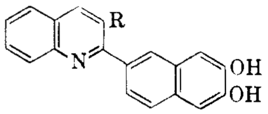


X R=CH_3
XI R=C_2H_5

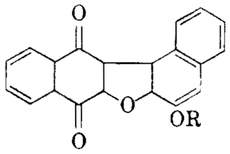


XII R=CO_2H, R'=H
XIII R=CO_2H, R'=CH_3
XIV R=R'=H
XV R=H, R'=CH_3

Several heterocyclic compounds derived from 2,3-dihydroxynaphthalene were synthesized in the course of this work. The Pfitzinger condensation of 6-acetyl- and 6-propionyl-2,3-dimethoxynaphthalene with isatin readily yielded 2-(2,3-dimethoxy-6-naphthyl)cinchoninic acid (XII) and its 3-methyl homolog (XIII). These acids readily underwent thermal decarboxylation to 2-(2,3-dimethoxy-6-naphthyl)quinoline (XIV) and its 3-methyl homolog (XV), and these two bases were converted by pyridine hydrochloride to 2-(2,3-dihydroxy-6-naphthyl)quinoline (XVI) and 3-methyl-2-(2,3-dihydroxy-6-naphthyl)quinoline (XVII). Condensation of 2-hydroxy-3-methoxynaphthalene with 2,3-dichloro-1,4-naphthoquinone in the presence of pyridine afforded 6-methoxydinaphtho[2,1-2',3']furan-8,13-dione (XVIII), which was demethylated in the usual way to 6-hydroxydinaphtho[2,1-2',3']furan-8,13-dione (XIX), a compound which cannot be synthesized by direct condensation of 2,3-dichloro-1,4-naphthoquinone with 2,3-dihydroxynaphthalene.[7] The hydroxy compounds reported are being tested on mice in this Institute by Dr. F. Duplan for protective activity against X-irradiation.



XVI R=H
XVII R=CH_3



XVIII R=CH_3
XIX R=H

EXPERIMENTAL

Formylation of 2,3-dimethoxynaphthalene. 2,3-Dimethoxynaphthalene was prepared by methylation of 2,3-dihydroxynaphthalene (100 g.) with dimethyl sulfate (181 g.) and potassium hydroxide (77 g.) in water; yield: 88 g. of the *diether*, b.p. 182°/17 mm., and 9 g. of *2-hydroxy-3-methoxynaphthalene*,[8] crystallizing from benzene in colorless needles, m.p. 108°.

A mixture of 45 g. of 2,3-dimethoxynaphthalene, 25 g. of dimethylformamide, and 42 g. of phosphorus oxychloride was heated on the water-bath for six hours. A concentrated aqueous solution of sodium acetate then was added, the mixture was refluxed for 30 minutes, and the aldehyde which formed was taken up in benzene. The benzene solution was washed with dilute hydrochloric acid, then with water, and dried over sodium sulfate. The residue from evaporation of the solvent gave on vacuum-fractionation 12 g. of *1-formyl-2,3-dimethoxynaphthalene* (II), b.p. 214–215°/15 mm., crystallizing from ethanol in shiny colorless needles, m.p. 79°.

Anal. Calc'd for $C_{13}H_{12}O_3$: C, 72.2; H, 5.6. Found: C, 72.3; H, 5.8.

The corresponding *thiosemicarbazone* crystallized from acetic acid in cream-colored needles, melting at 221° and decomposing on prolonged heating above 210°.

Anal. Calc'd for $C_{14}H_{15}N_3O_2S$: N, 14.5. Found: N, 14.2.

2,3-Dimethoxy-1-methylnaphthalene (III). A mixture of 7.7 g. of the foregoing aldehyde, 3 g. of 95% hydrazine hydrate, and 100 ml. of diethylene glycol was heated until dissolution. After addition of 3 g. of potassium hydroxide, refluxing was resumed for 15 minutes with removal of water. Water was added on cooling, the reaction product taken up in benzene, and the benzene layer washed first with dilute hydrochloric acid, then with water, and dried over sodium sulfate. The residue from evaporation of the solvent yielded on vacuum-fractionation 6.5 g. of *2,3-dimethoxy-1-methylnaphthalene*, b.p. 177°/16 mm., crystallizing from petroleum ether (b.p. 40–65°) in silky colorless needles, m.p. 66°.

Anal. Calc'd for $C_{13}H_{14}O_2$: C, 77.2; H, 6.9. Found: C, 77.3; H, 6.9.

The corresponding *picrate* crystallized from ethanol in shiny, orange-yellow needles, m.p. 82°.

2,3-Dihydroxy-1-methylnaphthalene (IV). A mixture of 2.5 g. of 2,3-dimethoxy-1-methylnaphthalene and 15 g. of pyridine hydrochloride was refluxed for 10 minutes, and when cooled, water was added. The precipitate was collected, dried, and recrystallized from cyclohexane, giving a 90% yield of cream-colored needles, m.p. 106°, turning a deep blue color with ferric chloride in water (or ethanol); excess of ferric chloride produced a dark blue precipitate.

Anal. Calc'd for $C_{11}H_{10}O_2$: C, 75.9; H, 5.7. Found: C, 75.7; H, 5.7.

1-Phenyl-2-(2,3-dimethoxy-1-naphthyl)acrylonitrile (V). To a solution of 5 g. of 1-formyl-2,3-dimethoxynaphthalene and 3 g. of benzyl cyanide in warm ethanol, a few drops of a 20% aqueous solution of sodium hydroxide was added, and the mixture was left to stand for 15 minutes. The precipitate which formed on dilution with water was collected and recrystallized from ethanol, giving 4 g. of shiny, pale yellow needles, m.p. 149°; sulfuric acid produced a deep yellow coloration.

Anal. Calc'd for $C_{21}H_{17}NO_2$: C, 80.0; H, 5.4. Found: C, 79.8; H, 5.5.

8-Hydroxy-3-phenyl-5,6-benzocoumarin (VI). A solution of 1 g. of the acrylonitrile (V) in 10 g. of pyridine hydrochloride was refluxed for 15 minutes; water then was added, the mixture was refluxed for 5 more minutes, and the precipitate was collected after cooling. Recrystallization from aqueous acetic acid gave 0.5 g. of fine yellowish prisms, m.p. 231°, giving an orange sodium salt.

Anal. Calc'd for $C_{19}H_{12}O_3$: C, 79.2; H, 4.2. Found: C, 79.0; H, 4.3.

1-Allyl-2-hydroxy-3-methoxynaphthalene (VII). A mixture of 7.8 g. of 2-hydroxy-3-methoxynaphthalene, 3 g. of potassium hydroxide (dissolved in 30 ml. of ethanol), and 7 g. of allyl bromide was refluxed for 30 minutes. After addition of water, the reaction product was taken up in benzene, and the benzene layer was washed with water and dried over sodium sulfate. The residue from evaporation of the solvent was half-solid and partly alkali-soluble, and was therefore vacuum-distilled. Yield: 5 g. of a product, b.p. 197–198°/15 mm., which was almost entirely soluble in an aqueous solution of sodium hydroxide. The alkali-soluble portion crystallized from petroleum ether (b.p. 40–60°) in colorless needles, m.p. 80°. This substance was unchanged after refluxing its solution for 4 hours in dimethylaniline.

Anal. Calc'd for $C_{14}H_{14}O_2$: C, 78.5; H, 6.5. Found: C, 78.7; H, 6.5.

Demethylation with pyridine hydrochloride yielded a substance which crystallized from ligroin in cream-colored needles, m.p. 130°, giving a greenish-blue coloration with

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(7) Buu-Hoï, *J. Chem. Soc.*, 489 (1952).

(8) Friedländer, *Monatsh.*, **23**, 973 (1902).

ferric chloride in ethanol. This compound probably was a coumarane derivative,[9] since all 2,3-dihydroxynaphthalene homologs give a deep blue coloration in this test.

6-Acetyl-2,3-dimethoxynaphthalene (VIII). To an ice-cooled solution of 20 g. of 2,3-dimethoxynaphthalene and 9.5 g. of acetyl chloride in 125 ml. of nitrobenzene, 16 g. of aluminum chloride was added in small portions with stirring. The mixture was kept overnight at room temperature, then poured into dilute hydrochloric acid, the nitrobenzene removed by steam-distillation, and the reaction product taken up in benzene. The benzene solution was washed with a 5% aqueous solution of sodium hydroxide, then with water, and dried over sodium sulfate; the residue from evaporation of the solvent yielded on vacuum-distillation 16 g. of a *ketone*, b.p. 237–238°/16 mm., crystallizing from ethanol in colorless prisms, m.p. 109°.

Anal. Calc'd for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1. Found: C, 72.9; H, 6.2.

6-Ethyl-2,3-dimethoxynaphthalene. Reduction of 10 g. of the foregoing ketone by means of 5 g. of hydrazine hydrate and 4 g. of potassium hydroxide in ethanol, performed as for III, yielded 6 g. of a product b.p. 200°/20 mm., crystallizing from ethanol in shiny colorless leaflets, m.p. 113°.

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

6-Ethyl-2,3-dihydroxynaphthalene (X). A mixture of 2 g. of the foregoing ether and 10 g. of pyridine hydrochloride was refluxed for 10 minutes. After dilution with water, the reaction product was taken up in ether, the ethereal solution washed with water and dried over sodium sulfate, and the solvent distilled off. The residue crystallized from benzene in colorless needles, m.p. 145°, giving a deep blue coloration with an aqueous solution of ferric chloride. Yield: 1.1 g.

Anal. Calc'd for $C_{12}H_{12}O_2$: C, 76.6; H, 6.4. Found: C, 76.9; H, 6.3.

2,3-Dimethoxy-6-propionaphthone (IX). Condensation of 6 g. of propionyl chloride with 11 g. of 2,3-dimethoxynaphthalene by means of 9 g. of aluminum chloride in nitrobenzene was performed as for the lower homolog (VIII). Yield: 11 g. of a *ketone*, b.p. 243–244°/17 mm., crystallizing from ethanol in colorless prisms, m.p. 102°.

Anal. Calc'd for $C_{15}H_{16}O_3$: C, 73.8; H, 6.6. Found: C, 73.7; H, 6.6.

2,3-Dihydroxy-6-n-propylnaphthalene (XI). Reduction of 7.5 g. of the foregoing ketone by means of 4 g. of hydrazine hydrate and 3 g. of potassium hydroxide afforded 4.5 g. of *2,3-dimethoxy-6-n-propylnaphthalene*, b.p. 206–207°/18 mm., crystallizing from ethanol in silky colorless needles, m.p. 79°.

Anal. Calc'd for $C_{15}H_{12}O_2$: C, 78.3; H, 7.8. Found: C, 78.0; H, 8.0.

2,3-Dihydroxy-6-n-propylnaphthalene, obtained by 10 minutes' heating of 2.5 g. of the foregoing ether with 15 g. of pyridine hydrochloride, crystallized from benzene in shiny colorless needles, m.p. 136°, giving a deep blue color in an aqueous solution of ferric chloride. Yield: 1.5 g.

Anal. Calc'd for $C_{13}H_{14}O_2$: C, 77.2; H, 6.9. Found: C, 77.0; H, 6.9.

Pfitzinger reaction with 2,3-dimethoxy-6-acetonaphthone. A solution of 4 g. of ketone (VIII), 2.8 g. of isatin, and 3 g. of potassium hydroxide in 30 ml. of ethanol was refluxed for 25 hours. After dilution with water and acidification with acetic acid, the precipitate of *2-(2,3-dimethoxy-6-naphthyl)-cinchoninic acid* (XII) was collected, and crystallized from ethanol. Yield: 5.8 g. of yellow prisms, m.p. 244°.

Anal. Calc'd for $C_{22}H_{17}NO_4$: C, 73.5; H, 4.7. Found: C, 73.2; H, 4.9.

Heating of this acid above its melting point, and vacuum-distillation of the residue, yielded *2-(2,3-dimethoxy-6-naphthyl)quinoline* (XIV), which crystallized from ethanol in pal yellow needles, m.p. 164°. Yield: 90%.

Anal. Calc'd for $C_{21}H_{17}NO_2$: N, 4.4. Found: N, 4.4.

The corresponding *monopicrate* crystallized from ethanol in deep yellow prisms, m.p. 203°.

Anal. Calc'd for $C_{27}H_{20}N_4O_9$: N, 10.2. Found: N, 10.0.

2-(2,3-Dihydroxy-6-naphthyl)quinoline (XVI). A mixture of 2 g. of the quinoline derivative (XIV) and 20 g. of pyridine hydrochloride was refluxed for 10 minutes. The yellow precipitate of the hydrochloride of (XVI) obtained on addition of water was collected, and treated with dilute aqueous ammonia to *p*H 7. The cream-colored substance (1.5 g.) crystallized from ethanol in colorless needles, m.p. 281°, giving a yellow solution in aqueous sodium hydroxide.

Anal. Calc'd for $C_{19}H_{13}NO_2$: N, 4.9. Found: N, 4.7.

Pfitzinger reaction of 2,3-dimethoxy-6-propionaphthone. A solution of 2 g. of the ketone (IX), 1.3 g. of isatin, and 1.4 g. of potassium hydroxide in 30 ml. of ethanol was refluxed for 44 hours. The usual treatment afforded 1.5 g. of *3-methyl-2-(2,3-dimethoxy-6-naphthyl)cinchoninic acid* (XIII), which crystallized from ethanol in almost colorless needles, m.p. 286°.

Anal. Calc'd for $C_{23}H_{19}NO_4$: C, 74.0; H, 5.1. Found: C, 73.7; H, 5.1.

Thermal decarboxylation yielded a base, which did not crystallize and which was treated with picric acid in ethanol. *3-Methyl-2-(2,3-dimethoxy-6-naphthyl)quinoline picrate* crystallized from ethanol in shiny yellow needles, m.p. 155°. Demethylation of this base with pyridine hydrochloride yielded *3-methyl-2-(2,3-dihydroxy-6-naphthyl)quinoline* (XVII), crystallizing from benzene in colorless needles, m.p. 126° containing crystallization-solvent; the pure compound, obtained on heating above 126°, melted at 220°.

Anal. Calc'd for $C_{20}H_{15}NO_2$: N, 4.7. Found: N, 4.7.

6-Methoxydinaphtho[2,1-2',3']furan-8,13-dione (XVIII). A solution of 1 g. of 2-hydroxy-3-methoxynaphthalene and 1.3 g. of 2,3-dichloro-1,4-naphthoquinone in 10 ml. of dry pyridine was refluxed for 15 minutes. After cooling, methanol was added, and the precipitate collected, dried, and recrystallized from nitrobenzene. Yield: 1.2 g. of wine-red, shiny, sublimable needles, m.p. 283°, giving blue solutions in sulfuric acid.

Anal. Calc'd for $C_{21}H_{12}O_4$: C, 76.8; H, 3.7. Found: C, 76.5; H, 3.5.

6-Hydroxydinaphtho[2,1-2',3']furan-8,13-dione (XIX). A mixture of 1 g. of the foregoing compound and 10 g. of pyridine hydrochloride was refluxed for 10 minutes. After dilution with water, the precipitate obtained was dried and crystallized from nitrobenzene, giving dark red needles melting above 345°; blue solutions in sulfuric acid.

Anal. Calc'd for $C_{20}H_{10}O_4$: C, 76.4; H, 3.2. Found: C, 76.5; H, 3.1.

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[9] See for instance, Hill, Short, and Stromberg, *J. Chem. Soc.*, 937 (1937).