needles which showed no change when heated at 300°. The acid is insoluble in alcohol and dissolves immediately in hydrochloric acid.

Anal. Calcd. for $C_5H_5O_2N_3$: N, 30.21. Found: N, 30.27, 20.15.

This same new pyrimidine acid is also formed by boiling a strong hydrochloric acid solution of its ethyl ester.

Summary

1. Diethyl ethoxymethylene-malonate condenses with thiourea in alcohol solution and in the presence of sodium ethylate to give ethyl 2-thiouracil-5-carboxylate. This sulfur pyrimidine is desulfurized by interaction with chloroacetic acid giving a quantitative yield of uracil-5-carboxylic acid.

2. Benzylpseudothiourea condenses with diethyl ethoxymethylene-malonate to form ethyl 2-benzylmercapto-6-oxypyrimidine-5-carboxylate.

3. Diethyl ethoxymethylene-malonate interacts with formamidine-sulfinic acid in alkaline solution to give ureido-methylene-malonic ethyl ester, $NH_2CONHCH{=}C(COOC_2H_5)_2$.

4. An improved method for the preparation of ethyl 2,6-dichloropyrimidine-5-carboxylate has been described.

5. 2-Ethylmercaptopyrimidine-5-carboxylate has been prepared by a new method. This acid is converted into ethyl 2-chloropyrimidine-5-carboxylate by treatment with chlorine gas.

6. Ethyl 2-chloropyrimidine-5-carboxylate reacts with ammonia to form ethyl 2-aminopyrimidine-5-carboxylate. The latter yields on saponification 2-aminopyrimidine-5-carboxylic acid.

7. Reduction of ethyl 2,6-dichloropyrimidine-5-carboxylate by digestion with hydriodic acid gave 6-oxypyrimidine-5-carboxylic acid.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE MALLINCKRODT CHEMICAL WORKS]

A Study of Diethyl 1,4-Dihydroxy-2,3-naphthalate[1]

BY AUGUST H. HOMEYER AND V. H. WALLINGFORD

The chemistry of 1,4-oxygenated naphthalene derivatives has been studied extensively in recent years because of the antihemorrhagic activity of many members of the group. Yet comparatively little is known about the 1,4-dihydroxy derivatives of 2-naphthoic and 2,3-naphthalic acids. Diethyl 1,4-dihydroxy-2,3-naphthalate (I) was obtained in 5% yield by Schwerin[2] from the condensation of diethyl phthalate with diethyl succinate. The yield of the dihydroxy ester has been increased to 48% by use of an excess of diethyl phthalate and more suitable conditions for the reaction. This material being readily available, it was interesting to study its methylation and hydrolysis.

The mono- and dimethoxy derivatives (V and II) were prepared by the action of methyl iodide and sodium ethylate. The monomethoxy compound was converted smoothly to the dimethoxy derivative by the same reagents. When the dimethoxy compound was prepared directly from the dihydroxy ester (I), an oil was also produced which showed marked antihemorrhagic activity. This product was 2,3-dihydro-2,3-dimethyl-2,3-dicarbethoxy-1,4-naphthoquinone resulting from methylation of the β-keto ester form of compound I in the 2 and 3 positions. Its hydrolysis was accompanied by loss of carbon dioxide and 2,3-dimethyl-1,4-dihydroxynaphthalene was formed.

Hydrolysis of diethyl 1,4-dimethoxy-2,3-naphthalate (II) gave a stable dicarboxylic acid (III) which formed an anhydride (IV) on heating. The monomethoxy ester (V), however, lost carbon dioxide on hydrolysis yielding 1-hydroxy-4-methoxy-3-naphthoic acid (VI). Similarly, hydrolysis of the dihydroxy ester (I) was accompanied by loss of carbon dioxide giving 1,4-dihydroxy-2-naphthoic acid (VIII) which Russig[3] obtained by carbonation of the disodium salt of 1,4-dihydroxynaphthalene. The easy loss of carbon dioxide from these two naphthalic acids was surprising since other known naphthalic and dihydroxyphthalic acids that have come to our attention are stable and form anhydrides readily. Traces of substances believed to be dicarboxylic acids were mentioned by Schwerin[2] and Russig[3] but they were not characterized.

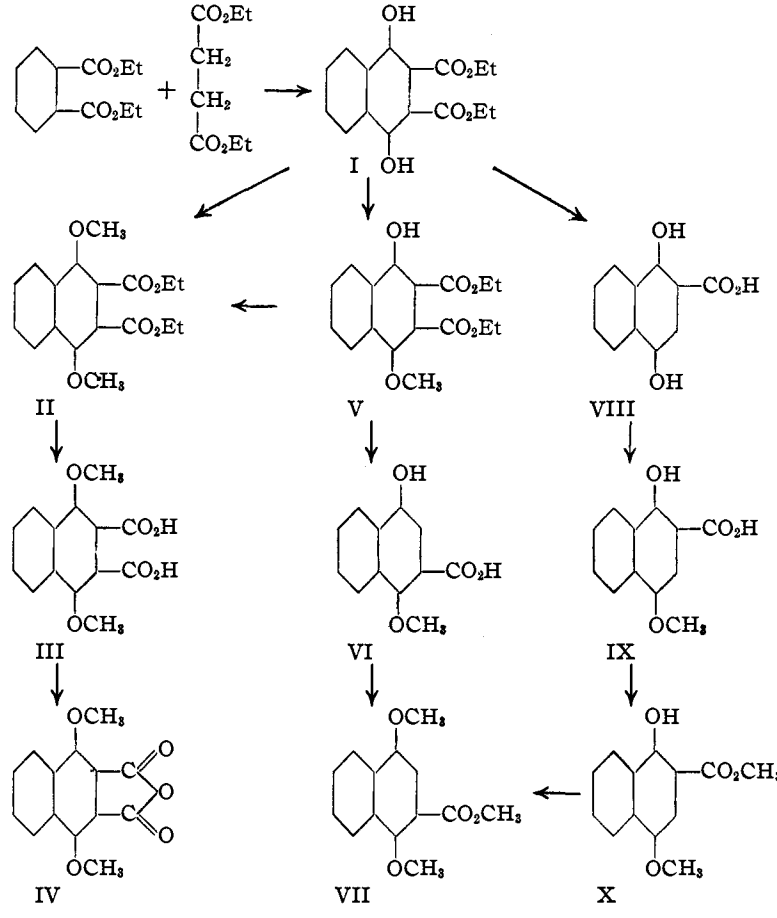
Methyl alcoholic hydrogen chloride converted 1,4-dihydroxy-2-napthoic acid (VIII) to its 4-

(1) Presented before the Division of Organic Chemistry at the Atlantic City meeting of the American Chemical Society, September 9, 1941.

(2) Schwerin, *Ber.*, **27**, 112 (1894).

(3) Russig, *J. prakt. Chem.*, [2] **62**, 33 (1900).

methyl ether (IX) and the ester of the latter (X) as described by Russig.[3] The acid (IX) differed from its isomer (VI). 1-Hydroxy-4-methoxy-2-naphthoic acid (IX) melted with decomposition at 196–198°, showed a bluish fluorescence in alcoholic solution, and gave a green color with ferric chloride. The isomeric 1-hydroxy-4-methoxy-3-naphthoic acid (VI), however, melted without decomposition at 217–218°, showed no fluorescence and gave no color with ferric chloride. The hydroxy acid (VI) was methylated smoothly by diazomethane to methyl 1,4-dimethoxy-3-naphthoate (VII). The isomer (IX), on the other hand, was converted smoothly by diazomethane only to its ester (X). Methylation of the hydroxyl of compound X by a large excess of diazomethane or sodium methylate and methyl iodide gave a poor yield of compound VII and considerable unreacted material was recovered. Hantzsch and Czapp[4] obtained ethyl 1-hydroxy-4-methoxy-2-naphthoate by ring enlargement of 2-carbethoxy-1,3-indandione with diazomethane. They reported diazomethane failed to methylate the hydroxyl in the 1-position. The difficulty of methylating this hydroxyl group is probably due to chelation with the adjacent ester group.



We are indebted to Dr. Robert Moore and Dr. Mary L. Miller, Washington University School of Medicine, for testing these compounds for antihemorrhagic activity. Essentially, the method of Ansbacher was employed. 2,3-Dihydro-2,3-dimethyl-2,3-dicarbethoxy-1,4-naphthoquinone showed the same order of activity as 2-methyl-1,4-naphthoquinone. None of the other compounds was active.

Experimental

Diethyl 1,4-Dihydroxy-2,3-naphthalate (I).—Sodium (24 g.) was dissolved in anhydrous alcohol (500 ml.) in a two-liter three-necked flask equipped with a mechanical stirrer, thermometer, dropping funnel and condenser arranged for distillation. After the sodium had dissolved, the flask was heated by an oil-bath and alcohol (310 ml.) was distilled off. Diethyl phthalate (400 ml.) was added and the mixture was stirred at 110–120° while diethyl succinate (88 g.) was added from the dropping funnel during about one and one-half hours. Heating was continued for three-quarters of an hour more. The sodium ethylate dissolved slowly and alcohol (200 ml.) was obtained as distillate. The reaction mixture became reddish in color and a solid separated.

After cooling the contents of the flask, water (500 ml.) was added to dissolve the solid and the oil was separated with the aid of benzene (300 ml.). The organic layer was extracted with dilute sodium hydroxide solution containing a little sodium hyposulfite. The aqueous solutions were combined and acidified with excess hydrochloric acid. The oily product was extracted with ether, and after evaporation of the solvent the reddish residue solidified. The product was dissolved in alcohol and crystallized by adding a little hydrochloric acid and ice. The yield of diethyl 1,4-dihydroxy-2,3-naphthalate was 48% (74 g.) based on diethyl succinate. It melted at 62–63°,[5] which agrees with the melting point given by Schwerin.[2]

An alcoholic solution of the product showed a bluish fluorescence, and a green color was produced by addition of ferric chloride. It reduced ammoniacal silver nitrate solution. After refluxing a sample (8 g.) with acetic acid

(4) Hantzsch and Czapp, *Ber.*, **63**, 566 (1930).

(5) The melting points reported in this paper are uncorrected.

(20 ml.) and concentrated hydrochloric acid (5 ml.) for three hours it was recovered unchanged. It was also recovered unchanged after refluxing for two hours with 3 molecular equivalents of sodium ethylate in alcohol.

Diethyl 1,4-Dimethoxy-2,3-naphthalate (II).—To a solution of sodium ethylate (5.5 g. sodium dissolved in 175 ml. of anhydrous alcohol) was added diethyl 1,4-dihydroxy-2,3-naphthalate (27 g.) and methyl iodide (40 g.). After refluxing five hours the solution was neutral to phenolphthalein. It was poured onto ice and hydrochloric acid and the oil was separated. The oil was dissolved in alcohol, cooled by solid carbon dioxide till it crystallized and the solid was washed with petroleum ether. The solid product (50% yield) was recrystallized from alcohol diluted with water. It melted at 48–49°, did not reduce ammoniacal silver nitrate solution, showed no fluorescence in alcohol, and gave no color with ferric chloride.

Anal. Calcd. for $C_{18}H_{20}O_6$: C, 65.0; H, 6.1. Found: C, 65.4; H, 6.0.

2,3-Dihydro-2,3-dimethyl-2,3-dicarbethoxy-1,4-naphthoquinone.—Evaporation of the alcohol–petroleum ether mother liquor from purification of compound II gave an oil which failed to crystallize. It distilled at 175–180° (3 mm.); $n^{20}D$ 1.541. Its antihemorrhagic activity was of the same order as 2-methyl-1,4-naphthoquinone. An alcoholic solution of the oil (2.7 g.) was hydrolyzed under an atmosphere of nitrogen by warming with sodium hydroxide (2.6 g.) dissolved in alcohol. The solution became dark red and a solid separated. The reaction mixture was blown into a mixture of hydrochloric and sulfurous acids; carbon dioxide was evolved and a solid (2,3-dimethyl-1,4-dihydroxynaphthalene) precipitated which was oxidized by air. The product was dissolved in acetic acid and the solution was filtered and diluted with water. The impure 2,3-dimethyl-1,4-naphthoquinone melted at about 120°. Crawford[6] gives 125–127°. The product was reduced and acetylated by heating at 120° with an excess of acetic anhydride and zinc dust for two hours. After recrystallization from absolute alcohol and sublimation in a high vacuum at 150–160°, the 2,3-dimethyl-1,4-diacetoxynaphthalene melted at 189–190°, which agrees with the melting point given by Crawford. The acetylated product, after warming with alcoholic sodium hydroxide and addition of sodium diethyl dithiocarbamate, gave the characteristic blue color reaction described by Irreverre and Sullivan[7] for 2,3-dimethyl-1,4-naphthoquinone.

1,4-Dimethoxy-2,3-naphthalic Acid (III).—The dimethoxy ester (II) (6.5 g.) was warmed with a solution of sodium hydroxide (4.5 g.) in water (10 ml.) and alcohol (40 ml.). The reaction mixture was poured onto ice and hydrochloric acid and the product was recrystallized from dilute alcohol. Neutral equivalent calcd. for $C_{14}H_{12}O_6$: 138. Found: 137. When heated in a melting point tube water was lost and the anhydride melted at 203–204°. An alcoholic solution displayed a bluish fluorescence.

1,4-Dimethoxy-2,3-naphthalic Anhydride (IV).—The naphthalic acid (III) (5 g.) was heated in a large test-tube by an oil-bath. Water began to be evolved at about 120°, and the product melted at about 200°. No carbon dioxide was liberated. The anhydride (4.5 g.) was crystallized from benzene, and sublimed in a high vacuum at 130°. It melted at 203–204°.

Anal. Calcd. for $C_{14}H_{10}O_5$: C, 65.1; H, 3.9; methoxyl, 24.0. Found: C, 65.2; H, 4.0; methoxyl, 23.9.

A sample of the anhydride was heated with phenol and stannic chloride. A phthalein type indicator was produced.

Diethyl 1-Hydroxy-4-methoxy-2,3-naphthalate (V).—To a solution of sodium ethylate (1.4 g. of sodium dissolved in 150 ml. anhydrous alcohol) were added diethyl 1,4-dihydroxy-2,3-naphthalate (18 g.) and methyl iodide (7 ml.). After refluxing for four hours the reaction mixture was neutral to phenolphthalein and was poured onto ice and hydrochloric acid. The waxy yellow solid (18 g.) obtained was recrystallized from anhydrous alcohol. The product (13 g.) melted at 80–81°. The product did not actively reduce ammoniacal silver solution. Its alcoholic solution showed a bluish fluorescence and became green on addition of ferric chloride.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 64.1; H, 5.7. Found: C, 64.1; H, 5.6.

Dilution of the alcoholic mother liquor with water gave an oil (4 g.) which was not further investigated.

The hydroxy methoxy compound (6.3 g.) was methylated smoothly by methyl iodide and sodium ethylate. The diethyl 1,4-dimethoxy-2,3-naphthalate (6.0 g.) produced melted at 47–48° and a mixture with material described above showed no depression of the melting point.

1-Hydroxy-4-methoxy-3-naphthoic Acid (VI).—Diethyl 1-hydroxy-4-methoxy-2,3-naphthalate was recovered unchanged after standing overnight with dilute sodium hydroxide at room temperature. The ester (6.5 g.) was refluxed two hours with a solution of sodium hydroxide (5 g.) in water (75 cc.) and kept overnight at 70°. When poured onto ice and hydrochloric acid, carbon dioxide was evolved and a solid separated. After recrystallization from diluted alcohol, it melted at 217–218°. It did not reduce ammoniacal silver solution, showed no fluorescence in alcohol, and gave no color with ferric chloride.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.1; H, 4.6. Found: C, 66.1; H, 4.5.

Methyl 1,4-Dimethoxy-3-naphthoate (VII).—1-Hydroxy-4-methoxy-3-naphthoic acid (1.1 g.) dissolved in a mixture of ether (75 ml.) and methanol (15 ml.) was treated with diazomethane (4 equivalents). On the following day the ether solution was washed with dilute hydrochloric acid, dilute sodium hydroxide and water. The solvent was evaporated and the residue was crystallized from diluted methanol and then sublimed in a high vacuum at 75°. The product (0.9 g.) melted at 57–59°.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.3; H, 5.7; methoxyl, 37.8. Found: C, 68.3; H, 5.6; methoxyl, 37.1.

1,4-Dihydroxy-2-naphthoic Acid (VIII).—Diethyl 1,4-dihydroxy-2,3-naphthalate (24 g.) was dissolved in a solution of sodium hydroxide (24 g.) and sodium hyposulfite (0.5 g.) in water (100 ml.) and kept in a stoppered flask overnight. The orange colored solution was poured onto ice and concentrated hydrochloric acid (40 ml.). Carbon dioxide was evolved and a yellow solid separated. The product was purified by recrystallization from diluted alcohol or from glacial acetic acid; from the latter solvent it

(6) Crawford, THIS JOURNAL, **57**, 2000 (1935).

(7) Irreverre and Sullivan, *Science*, **94**, 498 (1941).

separated with acetic acid of crystallization. The yield was 87% (14 g.). It melted with decomposition at about 200° compared to 186° given by Russig.[3] Neutral equivalent calcd. for $C_{11}H_8O_4$: 204. Found: 199. It reduced ammoniacal silver nitrate, displayed a bluish fluorescence in alcoholic solution and gave a green color with ferric chloride.

Refluxing a sample (1 g.) with acetic anhydride (10 ml.) and sodium acetate (0.5 g.) for one and one-half hours yielded 1,4-diacetoxy-naphthalene as described by Russig.[3] The reaction mixture was stirred with water to decompose excess acetic anhydride and the product was extracted with ether. After evaporation of the solvent, the product was crystallized from diluted alcohol. It melted at 124–125°.

1-Hydroxy-4-methoxy-2-naphthoic Acid (IX).—A solution of 1,4-dihydroxy-2-naphthoic acid (20 g.) in methanol (280 g.) was saturated with hydrogen chloride and warmed on a steam-bath for three hours. Considerable solid separated from the solution, and after cooling it was saturated again with hydrogen chloride. On the following day the reaction mixture was poured into water and the solid was washed with water and dried; weight 22 g. The product was agitated with a dilute solution of sodium bicarbonate which dissolved part of the solid with liberation of carbon dioxide. The undissolved solid was extracted with ether, the extract being saved for recovery of methyl 1-hydroxy-4-methoxy-2-naphthoate.

The aqueous layer was acidified yielding a solid weighing 16.5 g. After recrystallization from acetic acid and then from diluted alcohol, the 1-hydroxy-4-methoxy-2-naphthoic acid was obtained as a pale yellow solid which melted with decomposition at 196–198° compared to 178° given by Russig,[3] and 180° given by Hantzsch and Czapp.[4] Its alcoholic solution showed a bluish fluorescence and gave a green color with ferric chloride.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.1; H, 4.6; neutral equivalent, 218. Found: C, 66.4; H, 4.6; neutral equivalent, 213.

Methyl 1-Hydroxy-4-methoxy-2-naphthoate (X).—The ether extract from the sodium bicarbonate treatment in the preceding preparation was evaporated to dryness; weight 7 g. After crystallization from a mixture of methanol and acetic acid and then from acetone, the melting point was 137–138° compared to 134° given by Russig.[3] After sublimation in a high vacuum at 90° the melting point was unchanged. The product appeared to be sensitive to air. It was insoluble in dilute ammonia, did not actively reduce ammoniacal silver nitrate, showed a bluish fluorescence in alcohol, and the alcoholic solution became pale green on addition of ferric chloride.

The same compound was obtained in good yield by methylation of 1-hydroxy-4-methoxy-2-naphthoic acid (IX) (1.1 g.) dissolved in a mixture of ether (100 ml.) and methanol (10 ml.) with diazomethane (4 equivalents). After standing overnight the ether solution was washed with dilute hydrochloric acid and then with water. Evaporation of the solvent gave a crude product (1 g.) which melted at 132–134°. After crystallization from acetone the melting point was 137–138° and showed no depression when mixed with the product described in the preceding paragraph.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.2; H, 5.2. Found: C, 67.2; H, 5.0.

Methylation of the product by a large excess of diazomethane or by methyl iodide and sodium methylate gave poor yields of methyl 1,4-dimethoxy-3-naphthoate (VII) and considerable unchanged material was recovered. The methylated product was identical with that obtained smoothly by the action of diazomethane on 1-hydroxy-4-methoxy-3-naphthoic acid.

Summary

Diethyl 1,4-dihydroxy-2,3-naphthalate has been prepared in 48% yield. Methylation gave the mono- and dimethoxy derivatives (V and II). Hydrolysis of the dimethoxy ester gave a stable naphthalic acid (III) while the esters having free hydroxyl groups lost carbon dioxide giving naphthoic acids (IX and VI). The acid (VI) was methylated smoothly by diazomethane to the dimethoxy ester (VII), while its isomer (IX) was esterified easily but the hydroxyl group was difficult to methylate.

ST. LOUIS, MO. RECEIVED DECEMBER 8, 1941