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The Phthaleins from Phenol and 1,2-Naphthalenedicarboxylic Acid

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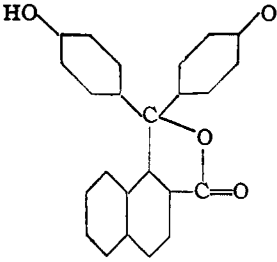
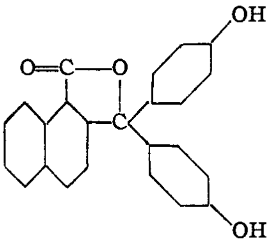
A study is being made in this Laboratory of the relationship, if any, between the molecular structure of aromatic compounds, especially of phthaleins, and their laxative potency.[1] Of the four theoretically possible phenolnaphthaleins, only one is known, the phenol-1,8-naphthalein.[2] Therefore, the synthesis of the phthaleins from phenol and 1,2-naphthalenedicarboxylic acid anhydride was undertaken. The two theoretically possible phthaleins were obtained. The main product (I) melted at 292° and yielded, on fusion with potassium hydroxide, 2-naphthoic acid and 4,4'-dihydroxybenzophenone. It is, therefore, the γ-lactone of the 1-(α,4,4'-trihydroxybenzohydryl)-2-naphthoic acid or the phenol-2,1-naphthalein. The by-product (II) melted at 268° and yielded, on treatment with potassium hydroxide, the 1-naphthoic acid and 4,4'-dihydroxybenzophenone. Therefore, it must be the γ-lactone of the 2-(α,4,4'-trihydroxybenzohydryl)-1-naphthoic acid or the phenol-1,2-naphthalein.



I



II

According to Dr. W. W. Hartman, the pH range for both phthaleins is approximately identical, 8.6 to 10.5, the color change from colorless to red magenta. Based on the color density curves, compound I is about four times more intense in color than II. The tests indicate that phenol-2,1-naphthalein (I) is the better indicator of the two, with the advantage over phenolphthalein that it does not fade.

In contrast to that of phenolphthalein and many other phthaleins,[3] the color of solutions of either of the two phthaleins in dilute alkali does not fade. Likewise, phenol-2,1-naphthalein resists oxidation by hydrogen peroxide, while phenolphthalein is easily oxidized under the same conditions.

Acknowledgment.—The author is indebted to Dr. L. T. Capell of *Chemical Abstracts* for the nomenclature and to Dr. W. W. Hartman of the Eastman Kodak Company for the preparation of the transmission curves.

Experimental[4]

Condensation of 1,2-Naphthalenedicarboxylic Anhydride with Phenol.—To 19.8 g. (0.1 mole) of 1,2-naphthalenedicarboxylic anhydride (m. p. 164–169°)[5] and 18.8 g. (0.2 mole) of phenol was added 8 ml. of stannic chloride and the mixture stirred for four hours at 113–116°. The reaction mass was treated with hot 0.1 *N* hydrochloric acid, filtered, and the residue dissolved in 300 ml. of 1 *N* sodium hydroxide. The red filtrate was saturated with carbon dioxide. The precipitated crude phthaleins weighed 16.4 g. (m. p. 240–270°). Separation into two compounds was effected by crystallization from acetic acid. The first crop consisted of the main product (I), crystallizing in fine needles arranged in star-like clusters. The by-product (II) was separated from subsequent fractions in the form of coarse, granular crystals. On heating a solution containing crystals of both compounds, the fine crystals of I dissolve first. This observation can be helpful in the separation; yield of I, 8.03 g. (22%) of m. p. 288–291°; of II, 1.82 g. (5%) of m. p. 261–267°.

Phenol-2,1-naphthalein.—Phthalein I was recrystallized for analysis from acetic acid (1 g. in 20 ml.) or from ethanol (1 g. in 4.5 ml.). It melts at 291.1–292.4°. One gram dissolves in 6.7 ml. of methanol (100%) and 16.5 ml. of ethanol (92.3%) at 20°. A 0.001 molar solution of I in 0.1 *N* sodium hydroxide is red magenta in color[6] or similar to that of a phenolphthalein solution of the same concentration. The solution has a maximum absorption at 562 λ. The color of such an alkaline solution, as well as that of phenol-1,8-naphthalein[2] in the same concentration, does not fade.[3] A 0.1 molar solution of I in 5 *N* sodium hydroxide is dark red and remains unchanged for months; a phenolphthalein solution of the same concentration turns to light red within a few minutes.

The color of I in concd. sulfuric acid is red.

Phenol-2,1-naphthalein turns from colorless to red at a pH of 8.6 to 10.5 or at a slightly higher pH than phenolphthalein. It is about one-third as strong in color as phenolphthalein and four times as strong as phenol-1,2-naphthalein (see Fig. 1).

By methylation of I with methyl iodide or dimethyl sulfate, an alkali-insoluble, non-crystallizable product was obtained.

Phenol-2,1-naphthalein could not be made to react with hydrogen peroxide, whereas phenolphthalein, under similar conditions, is oxidized readily.[3] Nor did I react with hydroxylamine.

Anal. Calcd. for $C_{24}H_{16}O_4$: C, 78.24; H, 4.37; mol. wt., 368. Found: C, 77.97; H, 4.34; mol. wt., 388, 366, 377, 322 (Signer method[7]).

Phenol-1,2-naphthalein.—The by-product was purified further by recrystallizations from acetic acid (1 g. in 16 ml.)

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[1] S. Loewe and M. Hubacher, *Arch. intern. pharmacodynamie*, **66**, 297 (1941); M. H. Hubacher, THIS JOURNAL, **64**, 2538 (1942).

[2] H. P. Kaufmann, *Z. angew. Chem.*, **40**, 863 (1927); F. F. Blicke and R. A. Patelski, THIS JOURNAL **60**, 2284 (1938).

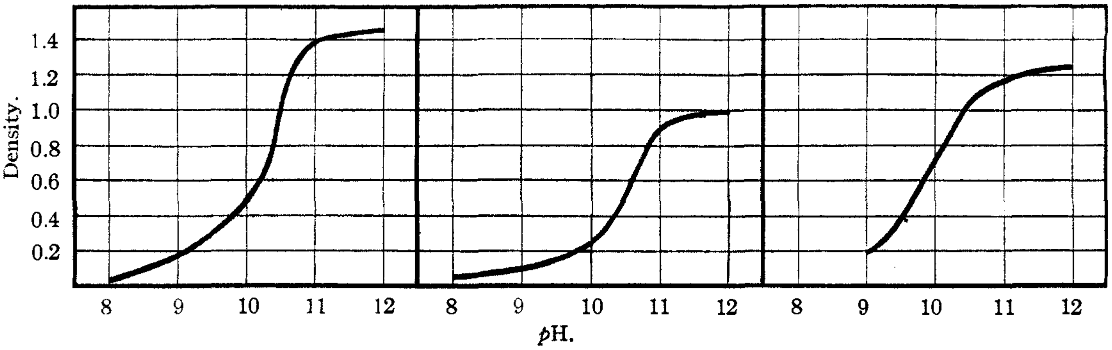
[3] M. H. Hubacher, *ibid.*, **65**, 2097 (1943).

[4] All melting points are corrected and determined in a Hershberg precision melting point apparatus. Before analysis, the compounds were dried to constant weight at 110° and 10 microns pressure, with the exception of the dipropionate of II, which was dried at 80° and high vacuum. Analyses by William Saschek.

[5] E. B. Hershberg and L. F. Fieser, "Organic Syntheses," Vol. **18**, 59 (1938).

[6] This color is called strong red or 4 R 4.5/18, according to the nomenclature of the Munsell Color System ("Method of Designating Colors," National Bureau of Standard Research Paper, RP 1239, Sept., 1939).

[7] E. P. Clark, *Ind. Eng. Chem., Anal. Ed.*, **13**, 820 (1941). Acetone was used as a solvent and azobenzene as a standard.



Phenol-2,1-naphthalein (I), 1:21,000, 1-cm. layer at λ 562. Phenol-1,2-naphthalein (II), 1:7,666, 1-cm. layer at λ 558. Phenolphthalein, 1:70,000, 1-cm. layer at λ 555.

Fig. 1.—Density-*p*H range characteristics.

and finally from ethanol. It melts at 267.5-269.5°. The color of a 0.001 molar solution in 0.1 *N* sodium hydroxide is red magenta[6] and orange in concd. sulfuric acid. The maximum of absorption is at 558 λ.

Anal. Calcd. for $C_{24}H_{16}O_4$: C, 78.24; H, 4.37; mol. wt., 368. Found: C, 78.06; H, 4.08; mol. wt., 352 (Rast in camphor).

Some 1,2-naphthalenedicarboxylic anhydride (8.1 g., m. p. 168-169°) was recovered from the mother liquor of the crude phthalein by acidification and sublimation of the precipitate at 160° in high vacuum.[8]

Fusion of I with Potassium Hydroxide.—Twenty grams of potassium hydroxide was heated in a nickel crucible to 240-245° (oil-bath temperature) and then 3.0 g. of I stirred in. After ten minutes, the melt was dissolved in water and treated for the separation of phenolic and acidic compounds by the usual method. The phenolic fraction was purified by sublimation at 180° and 20 microns pressure,[8] yielding 0.697 g. (40%) of 4,4′-dihydroxybenzophenone melting at 208-214° (no depression when mixed with a pure specimen of m. p. 216.8-217.2°).[9] The acidic fraction, likewise purified by sublimation at 150° and 10 microns, weighed 1.006 g. (72%) and melted at 181.5-184.4° (no depression when mixed with 2-naphthoic acid (Eastman Kodak Co.) of m. p. 183.2-184.8°).

Fusion of II with Potassium Hydroxide.—Seven grams of potassium hydroxide was stirred with 0.726 g. of II (m. p. 260-265°) for ten minutes at 240-245° (oil-bath temperature). The reaction product consisted of 0.270 g. (64%) of 4,4′-dihydroxybenzophenone (m. p. 208-215°) and 0.279 g. (82%) of 1-naphthoic acid (m. p. 161.7-162.8°) (no depression when mixed with 1-naphthoic acid (Eastman Kodak Co.) of m. p. 159.8-161.1°).

Acetyl Derivative of I.—A solution of 1.84 g. (0.005 mole) of I, 1.50 g. (0.015 mole) of acetic anhydride, 5 ml. of acetic acid and one drop of concd. sulfuric acid was refluxed for one hour. The product weighed 2.22 g. (98%, m. p. 218-223°) and after two crystallizations from ethanol (1 g. in 100 ml.) melted at 223.8-225.9°.

Anal. Calcd. for $C_{28}H_{20}O_6$: C, 74.32; H, 4.46; mol. wt., 452. Found: C, 74.01; H, 4.52; mol. wt., 435, 409, 460 (Signer method[7]).

Propionyl derivative of I was prepared by refluxing for one hour 0.92 g. of I, 3.0 ml. of propionic anhydride and a trace of concd. sulfuric acid. The crude product was recrystallized from 20 ml. of ethanol, yielding 0.94 g. (78%, m. p. 159-162°). The pure compound melted at 162.7-163.7°.

Anal. Calcd. for $C_{30}H_{24}O_6$: C, 74.97; H, 5.04. Found: C, 74.99; H, 5.13.

Acetyl derivative of II was prepared as was the acetyl derivative of I, from 0.368 g. of II (m. p. 260-264°). The crude material was recrystallized three times from ethanol, the purified product melting at 154.5-155.6°.

Anal. Calcd. for $C_{28}H_{20}O_6$: C, 74.32; H, 4.46. Found: C, 74.11; H, 4.41.

Propionyl derivative of II was prepared as was the propionyl derivative of I, and purified by crystallizations from ethanol; it melted at 109.6-111.0°.

Anal. Calcd. for $C_{30}H_{24}O_6$: C, 74.97; H, 5.04. Found: C, 74.59; H, 4.83.

Summary

The two theoretically possible phthaleins from phenol and 1,2-naphthalenedicarboxylic acid anhydride were prepared and their structure proved. The corresponding acetyl and propionyl derivatives were made also.

BROOKLYN, N. Y. RECEIVED SEPTEMBER 17, 1943

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[8] In tube A of the apparatus described in *Ind. Eng. Chem., Anal. Ed.*, **15**, 448 (1943).

[9] Prepared according to A. Baeyer and J. B. Burkhardt, *Ann.*, **202**, 126 (1880).