ploying pyridine,[7] gave a mixture which was separated through distillation and recrystallization into two isomeric compounds considered to be 9-keto-$\Delta^{1,10}$-decahydrophenanthrene (II) and *sym*-octahydro-9-phenanthrol (III).

Mixed melting point determinations showed that I, II and III were distinct. Although neither product gave a positive ferric chloride test, the phenolic compound (III) was slightly soluble in 10% sodium hydroxide solution and had the same melting point as the previously described III prepared by different procedures.[8] Also, the infrared absorption spectrum of III showed a strong peak at 3.13 μ, indicative of a hydroxyl, and weaker peaks at 6.20, 6.32, and 6.67, indicative of a monohydroxyphenyl grouping. II showed strong carbonyl absorption (6.13 μ) in the infrared and absorption of less intensity at 6.33 suggestive of conjugated C=C groupings. Absorption maximum of II in the ultraviolet was at 286 mμ, which compares favorably with the value of 280 calculated by the rule of Woodward and found for the analogous $\Delta^{3,5}$-cholestadiene-7-one.[9] It is possible that II may have a double bond between positions 4 and 4a instead of 1 and 2. However, Woodward's rule gives 298, a less favorable value than 280.

The isolation of compounds of structures II and III suggests that the allylic bromination of I occurred at positions 1 and 4a. II probably arises from loss of hydrogen bromide at positions 1 and 2 and III from loss at 4a and 5a.

EXPERIMENTAL

Reaction of trans-9-keto-Δ^{10}-dodecahydrophenanthrene (I) *with N-bromosuccinimide.* A mixture of 6 g. (0.029 mole) of I, 15.8 g. (0.066 mole) of *N*-bromosuccinimide and 100 ml. of carbon tetrachloride was heated at reflux temperature for 90 min. The solvent was removed by distillation and replaced with 100 ml. of pyridine, whereupon heating at boiling temperature was continued for 2 hr. The pyridine was removed under reduced pressure and the residue dissolved in ether. After the ether extract was washed with 2*N* hydrochloric acid and then water, it was dried over magnesium sulfate and the ether removed. Upon distillation of the residue, 3 g. of crude 9-keto-$\Delta^{1,10}$-decahydrophenanthrene (II) was obtained at 145–150° (0.2 mm.). The solidified residue was recrystallized first from methyl alcohol and then from acetone, m.p. 119–121° (λ_{max}^{EtOH} 286 mμ, ϵ 1 × 10^4; λ_{min}^{EtOH} 270 mμ).

Anal. Calcd. for $C_{14}H_{16}O$: C, 83.11; H, 8.97. Found: C, 83.03; H, 9.55.

Continued distillation at 150–155° (0.2 mm.) gave 1 g. of oil which solidified. After removal of the mother liquors from the isolation of II, the residue was combined with the solid distillate and distilled to give 2.1 g. of solid product, b.p. 155° (0.2 mm.). Upon recrystallization from methyl alcohol, a small amount of II separated. On standing, the filtrate yielded a higher melting compound. Recrystallization from dilute methyl alcohol gave a small amount of *sym*-octahydro-9-phenanthrol (III), m.p. 133–134° (lit.[8] 133°).

Anal. Calcd. for $C_{14}H_{16}O$: C, 83.11; H, 8.97. Found: C, 83.66; H, 9.12.

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The Synthesis of 7-Halogeno-1-hydroxy-2-naphthoic Acids

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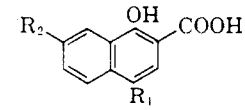
This report deals with the preparation of 1-naphthol derivatives with substitutions in the difficultly accessible 7-position.[1,2] The procedure employed for the preparation of the desired compounds involved the cyclization of a γ-substituted phenylbutyric acid to a 7-substituted-1-tetralone, followed by bromination and dehydrobromination to the naphthol. This product was carboxylated by a modified Kolbe procedure with subsequent chlorination in the 4-position.

Although somewhat lengthy, the procedure adopted has given unequivocally the desired modified naphthoic acids. Of special interest is the action of dimethyl formamide and lithium chloride as a dehydrohalogenating agent. This reagent was employed by Holyz[3] for introducing α, β-unsaturation in 3-keto steroids, and has recently been used by Gabel and Binkley[4] in the dehydrobromination of bromodihydropyrimidines to pyrimidines. The present application to bromotetralones indicates the general usefulness of this method. According to Holyz the lithium chloride is an obligatory factor for the activation of the bromine atom.

Four new 1-hydroxy-2-naphthoic acids have been synthesized and characterized. The effect of these



R_1 = hydrogen or chlorine
R_2 = bromine or chlorine

compounds and their derivatives on oxidative phosphorylation in rat brain mitochondria was studied and it was observed that both a free carboxyl group and a free hydroxyl group were necessary for inhibition of this process.

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EXPERIMENTAL

All melting points are uncorrected. Carbon and hydrogen analyses were made by Spang Microanalytical Laboratories, Ann Arbor, Mich.

3,4-Dihydro-7-halo-1(2H)naphthalenones. These tetralones were prepared according to the procedure of Fieser and Seligman.[5]

2-Bromo-3,4-dihydro-7-halo-1(2H)naphthalenones. These compounds were prepared according to the procedures of Coulson,[6] and Fieser and Dunn.[7] These 2-bromo-1-tetralones are very irritating to the skin.[8] Prolonged contact can lead to severe dermatitis.

7-Halo-1-naphthols.[9] Lithium chloride (3.23 g., 0.0762 mole) was dissolved in dimethylformamide (75 ml.) by heating to 70–80°. 7-Chloro-2-bromo-3,4-dihydro-1(2H)-naphthalenone (6.6 g., 0.025 mole) was dissolved in dimethylformamide (25 ml.) and added to the lithium chloride solution. This resulting solution was heated on a steam bath for 3.5 hr. The solution was cooled and transferred to a separatory funnel. Ether (150 ml.) was added and the dimethyl formamide and lithium chloride were extracted with a 75 ml. portion of water. The aqueous layer was diluted with an equal amount of water and extracted with 50 ml. of ether. The ether layers were combined and washed four more times with 75 ml. portions of water, dried over magnesium sulfate, filtered, and the ether removed *in vacuo*. The residue was recrystallized from hot benzene and the light tan needles were washed with petr. ether. Yield, 2.41 g. (56%) m.p. 120–122° (lit. 123° (2)). Picrate, m.p. 139–140° (Lit. 139° (2)).

2,7-Dibromo-3,4-dihydro-1(2H) naphthalenone (26 g., 0.085 moles) was dissolved in 150 ml. of dimethylformamide. Lithium chloride (10.9 g., 0.256 moles) was added and the solution was heated at reflux temperature for 120 hr. The product was obtained by following the procedure outlined above and recrystallized from benzene-petr. ether to give rose colored crystals which darkened upon standing. Yield, 14.5 g. (76%) m.p. 101–105° (lit. 105.5–106.5°[9]).

7-Halo-1-hydroxy-2-naphthoic acids. These acids were prepared according to the procedures of Baine *et al.*,[10] and Cameron *et al.*[11]

The 7-halogeno-1-naphthol was mixed with three equivalents of anhyd. potassium carbonate in a high pressure hydrogenation apparatus. Samples of naphthol from 1–10 g. were employed. The reaction was effected at 150° under 1500 p.s.i. of carbon dioxide for 4 hr. The cooled reaction charge was dissolved in hot water and filtered rapidly. Prolonged heating resulted in decarboxylation and formation of tars. The filtrate was acidified with 6*N* hydrochloric acid. The yields were consistently in the range of 65–70%.

7-Chloro-1-hydroxy-2-naphthoic acid was purified by solution in hot 95% alcohol and reprecipitation by the addition of water. Slow recrystallization did not remove the colored contaminant from the product. Three consecutive reprecipitations gave a product which decomposed with the evolution of carbon dioxide[12] at 212–213.5°. The acid gave a blue green color with ferric chloride. A determination of the neutralization equivalent gave a value of 224 (calcd. neut. equiv., 222.5).

Anal. Calcd. for $C_{11}H_7O_3Cl$: C, 59.34; H, 3.17. Found: C, 59.47; 59.55; H, 3.34; 3.38.

The methyl ester derivatives of the carboxylic acids were prepared by the reaction of excess diazomethane with the acids suspended in ether. The excess diazomethane does not attack the free hydroxyl group in the ortho position.[12] The esters were recrystallized from 95% ethanol. Methyl 7-chloro-1-hydroxy-2-naphthoate melted at 107°.

Anal. Calcd. for $C_{12}H_9O_3Cl$: C, 60.90; H, 3.83. Found; C, 61.04; 60.97; H, 3.97; 3.88.

7-Bromo-1-hydroxy-2-naphthoic acid was purified by slow recrystallization from aqueous ethanol to give a product which decomposed at 214.5–215°. Neut. equiv., 267 (Calcd. neut. equiv., 267).

Anal. Calcd. for $C_{11}H_7O_3Br$: C, 49.46; H, 2.64. Found: C, 49.56; 49.52; H, 2.86; 3.29.

Methyl 7-bromo-1-hydroxy-2-naphthoate m.p. 115–117°.

Anal. Calcd. for $C_{12}H_9O_3Br$: C, 51.27; H, 3.23. Found: C, 51.46; 5.35; H, 3.38; 3.29.

Methyl 1-acetoxy-7-bromo-2-naphthoate was prepared by heating isopropenyl acetate and methyl 7-bromo-1-hydroxy-2-naphthoate at reflux temperature in the presence of catalytic amounts of sulfuric acid. The product was recrystallized from absolute alcohol. M.p. 136–137°.

4-Chloro-7-halogeno-1-hydroxy-2-naphthoic acids.[13] 7-Chloro-1-hydroxy-2-naphthoic acid (3.5 g., 0.0157 mole) was treated at reflux temperature with about 20 ml. of glacial acetic acid in a 25 ml. three necked flask fitted with a stirrer, and condenser with a calcium chloride tube. Chlorine was passed over the surface of the stirred solution for about 20 min. whereupon the product precipitated. The solvent was evaporated and the residue was dissolved in sodium carbonate solution and filtered. The residue was extracted with dilute sodium hydroxide and filtered. The two filtrates were combined, decolorized with charcoal, filtered, and acidified with 6*N* hydrochloric acid. Yield, 1.0 g. (25%) m. 235–236° dec. This product was purified by reprecipitation from hot aqueous alcohol four times to give a compound which decomposed at 242°. Neut. equiv., 257 (Calcd. neut. equiv., 257).

Anal. Calcd. for $C_{11}H_6O_3Cl_2$: C, 51.39; H, 2.35. Found: C, 50.88; 50.94; H, 2.63; 2.71.

Methyl-4,7-dichloro-1-hydroxy-2-naphthoate. m.p. 155°.

Anal. Calcd. for $C_{12}H_8O_3Cl_2$: C, 53.16; H, 2.97. Found: C, 53.23; 53.29; H, 3.11; 3.15.

7-Bromo-1-hydroxy-2-naphthoic acid (2 g., 0.0075 mole) was chlorinated by the procedure described above. The product which had separated was removed by filtration and dissolved in 95% ethanol. The solution was decolorized with charcoal, filtered, and cooled, whereupon crystals formed. Yield, 1.83 g. (81%) dec. 240°. This compound was recrystallized twice from aqueous alcohol to give a product which decomposed at 249–250°. Neut. equiv., 298.5 (Calcd. neut. equiv., 301.5).

Anal. Calcd. for $C_{11}H_6O_3BrCl$: C, 43.81; H, 2.01. Found: 43.88; 43.89; H, 2.25; 2.19.

Methyl 7-bromo-4-chloro-1-hydroxy-2-naphthoate. m.p. 147–148°.

Anal. Calcd. for $C_{12}H_8O_3BrCl$: C, 45.67; H, 2.56. Found: C, 45.54; 45.59; H, 2.71; 2.62.

Acetate (acid) m.p. 184.5°.

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