[CONTRIBUTION FROM THE LABORATORIES OF G. D. SEARLE & CO.]

Synthetic Choleretics. I. Naphthol Derivatives[1]

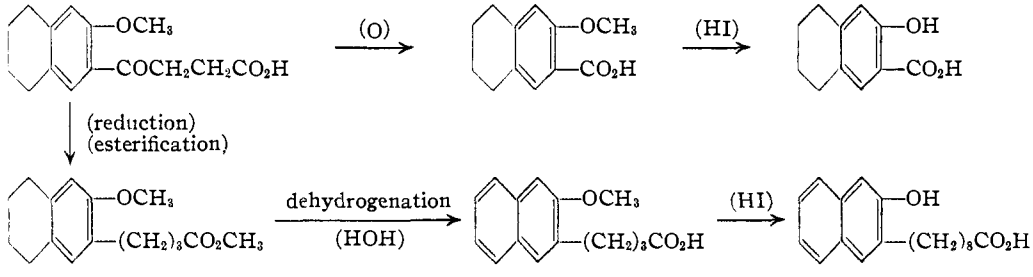
BY ROBERT R. BURTNER AND JOHN M. BROWN

Twenty-four derivatives of α- and β-naphthol, containing a γ-oxobutyric acid group and related substituents, were prepared and studied for choleretic activity in the dog. In the α-naphthol series the 2- and 4-positions of the substituents are approximately equivalent. A side chain consisting of the group $-COCH_2CH_2COOH$ is indicated for maximum activity. The corresponding *n*-propyl ketones possessing the same carbon skeleton are much less effective. Expansion of the alkylene group in the side chain to $(CH_2)_8$ sharply decreases activity. The carboxyl group should be free, as evidenced by the reduced potency of the methyl ester and the diethylamide. There is some evidence that the methyl ethers are more active than the corresponding phenolic compounds. The presence of a bromine atom or a second hydroxyl group in the nucleus does not enhance the effect. In the β-naphthol series maximum choleresis is obtained with the side chain in the 6-position, the 1- and 3-isomers being considerably less potent. Under the experimental conditions several of these compounds were approximately 50% more potent than dehydrocholic acid.

Choleretics are commonly defined[2] as agents which increase the volume output of bile by the liver and are not to be confused with cholagogs which merely promote expulsion of stored bile from the gallbladder. In recent years such substances have been widely used in the non-surgical treatment of several common pathological conditions of the biliary tract where flushing and drainage are indicated. The bile acids obtained from cattle and hogs have been most commonly employed in this type of therapy. The clinical utility of these choleretics, however, is impaired to some extent by certain undesirable side effects, primarily gastric disturbances. Furthermore, several economic factors such as greatly increased demands for animal bile, uncertainty of supply and quality of material have stimulated interest in a synthetic product. For these reasons the present study is being conducted in the search for a potent, synthetic choleretic with an improved quality of action.

The notable success of the stilbene type of synthetic estrogens strongly suggested the possibility that choleretic activity might reside in relatively simple, binuclear compounds bearing one or more phenolic hydroxyl groups and a butyric acid side chain. Sobotka[3] has reviewed the choleretic properties of a variety of phenolic compounds and carboxylic acids, which were reported by previous investigators. The activities of the naphthols and 2-hydroxy-3-naphthoic acid, as described by Chabrol and co-workers,[4] were of particular interest. In view of the ready availability of the naphthols and the ease with which a four carbon atom side chain can be introduced by the Friedel–Crafts reaction, these compounds were selected as starting materials.

The rather abnormal orientation of 2-alkoxy-5,6,7,8-tetrahydronaphthalene was first noted by Sergievskaya and Danilova.[5] These authors reported that 2-ethoxy-5,6,7,8-tetrahydronaphthalene reacted with succinic anhydride in the presence of aluminum chloride to give a mixture of two acids substituted at the 3- and 4-positions, respectively. The structures which they assigned to their products were based upon ring closure reactions to form the corresponding phenanthrene derivatives. Since the validity of this method is perhaps open to some question, we felt that a more positive proof of structure was indicated to establish the identity of our product. This was accomplished by the following sequence of reaction, arriving at known compounds in each instance.



Pharmacological Part

The pharmacological studies were conducted by Dr. Martin Gunter under the direction of Dr. A. C. Ivy at the University of Illinois and involved the use of the acute biliary fistula experiment on the dog under pentobarbital anesthesia. The common duct is cannulated and the cystic duct is clamped with a hemostat. A rubber tube attached to the cannula is brought to the outside through the abdominal incision. The bile is collected for a control period of thirty minutes. A predetermined amount of the unknown is administered intravenously as the sodium salt and the bile collected at thirty-minute intervals until the flow has returned to the control rate. The equivalent dose of dehydrocholic acid, the reference standard, is then determined from a dose–response curve based upon data secured from the previous study of one hundred dogs. The potency of the unknown is expressed in terms of per cent. activity referred to dehydrocholic acid to which the value of one hundred was arbitrarily assigned. Since all studies were conducted on a molar basis, it is necessary to multiply the "molar

(1) Presented before the Medicinal Division of the American Chemical Society at San Francisco, April, 1949.

(2) Brugsch and Horsters, *Klin. Wochenschr.*, **2**, 1538 (1923).

(3) Sobotka, "Physiological Chemistry of the Bile," Williams and Wilkins Co., Baltimore, Md., 1937.

(4) Chabrol, Charonnat, Maximin, Porin and Piettre, *Compt. rend. soc. biol.*, **101**, 254 (1929).

(5) Sergievskaya and Danilova, *J. Gen. Chem.* (*U. S. S. R.*), **16**, 1077 (1946).

activity" by the factor mol. wt. of dehydrocholic acid/mol. wt. of unknown to obtain the potency on a weight basis.[6]

Experimental Part

β-(1-Methoxy-4-naphthoyl)-propionic Acid.—Fieser and Hershberg[7] prepared this acid by the interaction of 1-methoxynaphthalene, succinic anhydride and aluminum chloride in *s*-tetrachloroethane at 0–5° for a 3-day period. The following procedure gives satisfactory yields in a much shorter time.

Two hundred and seventy-eight grams (2.08 moles) of aluminum chloride were added over a 30-minute period to a stirred suspension of 158 g. (1.0 mole) of 1-methoxynaphthalene and 104 g. (1.04 moles) of succinic anhydride in two liters of benzene. No attempt was made to control the temperature which rose to 60°. The mixture was stirred for 15 minutes and then refluxed with stirring for 1 hour. Hydrolysis of the hot, easily fluid mixture with ice and hydrochloric acid, followed by steam distillation of the solvent and *hot* filtration (to remove traces of the more soluble benzoylpropionic acid) gave the crude acid. This was purified by dissolving in 2.5 liters of 2% sodium hydroxide at about 85°, treating with Darco and slowly adding the cooled filtrate to a stirred excess of dilute hydrochloric acid. The yield of acid melting at 172–173° was 233 g. or 90% of theory.

This method has also been successfully used in the preparation of β-(5-acenaphthoyl)-propionic acid, eliminating thereby the use of nitrobenzene.

γ-(1-Methoxy-4-naphthoyl)-butyric Acid.—A stirred solution of 64.8 g. (0.41 mole) of 1-methoxynaphthalene and 47 g. (0.41 mole) of glutaric anhydride in 410 ml. of *s*-tetrachloroethane was treated portionwise at 0–2° with 109 g. (0.82 mole) of aluminum chloride. By the time half of the catalyst had been added a viscous, lumpy mass had formed, requiring manual stirring during the addition of the balance of the aluminum chloride. The mixture was then stored in the refrigerator for 4 days with occasional stirring. After hydrolysis the solvent was steam distilled and the dark somewhat tacky crude acid filtered from the cooled mixture. It was dissolved in one liter of 5% sodium carbonate, the solution washed with ether to remove neutral impurities and acidified to yield 58.8 g. of acid, m.p. about 163°. Crystallization from 900 ml. of methanol gave 42 g. of pale yellow crystals melting at 167°.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.92. Found: C, 70.6; H, 5.85.

δ-(1-Methoxy-4-naphthoyl)-valeric Acid.—A stirred solution of 100 g. (0.63 mole) of 1-methoxynaphthalene and 89.6 g. (0.7 mole) of adipic anhydride[8] in 700 ml. of *s*-tetrachloroethane was treated portionwise with 167.6 g. (1.26 moles) of aluminum chloride at 0–5°. The mixture was stirred for an additional 2 hours at 0° and then stored in the refrigerator for 5 days. Subsequent to hydrolysis and removal of solvent by steam distillation the dark, semi-solid crude was separated from the hot mother liquor by decantation. It was suspended in two liters of hot 4% sodium carbonate, cooled, the solution decanted from insoluble residue, washed with ether and acidified. The viscous precipitate, which became granular in about 20 minutes, was triturated with water, filtered and dried. Crystallization from 250 ml. of benzene (Darco) yielded 50 g. of acid melting at 114°.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.3; H, 6.34. Found: C, 71.5; H, 6.50.

ω-(Methoxy-4-naphthoyl)-pelargonic Acid.—Two hundred and thirty-four grams (1.76 moles) of aluminum chloride was added portionwise at 0–3° to a stirred solution of 127 g. (0.8 mole) of 1-methoxynaphthalene and 162 g. (0.88 mole) of sebacic anhydride[8] in 900 ml. of *s*-tetrachloroethane. After an additional 2 hours of stirring at 0° the mixture was placed in the refrigerator for 6 days. The slushy product was hydrolyzed, the solvent steam distilled and the *hot* supernatant liquor discarded. An extract of the crude in three liters of hot 3% sodium carbonate was centrifuged (filtration was extremely slow) and acidified to precipitate a soap-like acid which soon granulated. Two crystallizations from 500-ml. and 225-ml. portions of benzene gave 30 g. of sebacic acid.

The combined crystallization mother liquors were concentrated to a volume of about 400 ml. and diluted with one liter of boiling cyclohexane. Gradual cooling with constant stirring produced 56 g. of a sand colored acid, m.p. 95–96°, which upon recrystallization from 200 ml. of benzene (Darco) weighed 42 g. and melted at 103°.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.6; H, 7.6. Found: C, 73.3; H, 7.46.

β-(2-Methoxy-5,6,7,8-tetrahydro-3-naphthoyl)-propionic Acid.—A stirred suspension of 48 g. (0.3 mole) of 2-methoxy-5,6,7,8-tetrahydronaphthalene and 33 g. (0.33 mole) of succinic anhydride in 350 ml. of nitrobenzene was treated portionwise at 5° with 80 g. (0.6 mole) of aluminum chloride. The mixture was stirred for an additional hour at 5° and then stored in the refrigerator for 4 days. After hydrolysis and steam distillation of the solvent the dark crude acid was dissolved in one liter of 4% sodium carbonate at 85° and filtered with Darco and Celite. Acidification of the cooled filtrate precipitated a light brown, granular acid which was filtered, rinsed and dried (44 g.). Crystallization from 450 ml. of acetic acid (Darco) gave 19.2 g. of sand colored product melting at 173° with decomposition. A sample crystallized from methanol as colorless needles, m.p. 175° (dec.).

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.9; H, 6.97.

Proof of Structure of β-(2-Methoxy-5,6,7,8-tetrahydro-3-naphthoyl)-propionic Acid (a) By Oxidation.—An alkaline solution of sodium hypochlorite was prepared by diluting 175 ml. of Clorox (5.25% sodium hypochlorite) with 325 ml. of water containing 10 g. of sodium hydroxide. Five grams of the acid was added, which dissolved and reacted immediately with sufficient heat effect to raise the temperature to about 50°. The solution was heated at 65° for 20 minutes and then refluxed for 20 minutes. The cooled mixture was washed with ether to remove a few drops of an oily precipitate, the alkaline solution heated to remove residual ether and finally saturated with sulfur dioxide. The colorless, crystalline precipitate was filtered, rinsed and dried to give 2.3 g. of acid, m.p. 110°. Crystallization from cyclohexane (50 ml./g.) raised the melting point to 112°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.9; H, 6.79; CH_3O, 15.05. Found: C, 70.0; H, 6.86; CH_3O, 14.22.

Demethylation was effected by refluxing 1 g. of the above acid in a solution of 10 ml. of 47% hydriodic acid and 4 ml. of acetic anhydride for 10 minutes. Dilution with ice-water precipitated a colorless acid which, after filtration and drying, weighed 0.82 g. and melted at 178–179°. This was shown to be identical with an authentic sample of 2-hydroxy-5,6,7,8-tetrahydro-3-naphthoic acid by a mixed melting point determination.

(b) **By Dehydrogenation.**—A mixture of 27.8 g. of the acid, 56 g. of amalgamated 20-mesh zinc, 98 ml. of hydrochloric acid (sp. gr. 1.2), 5.6 ml. of acetic acid, 42 ml. of water and 56 ml. of toluene was refluxed for 24 hours. Three 27-ml. portions of hydrochloric acid were added at 6-hour intervals. A benzene extract of the cooled mixture was washed well with water and evaporated to yield 26.2 g. of a waxy crude acid. Crystallization from 125 ml. of cyclohexane gave 20.3 g. of dense, white crystals, m.p. 81–82°. A negative ferric chloride test indicated that no demethylation occurred during reduction.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; CH_3O, 12.50. Found: C, 72.89; H, 8.26; CH_3O, 12.14.

The methyl ester, obtained by treating the butyric acid with diazomethane, boiled at 160° at 0.4 mm., $n^{25}D$ 1.5268.

Anal. Calcd. for $C_{16}H_{22}O_3$: CH_3O, 23.62. Found: CH_3O, 23.29.

Nineteen grams of the ester was dehydrogenated by heating at 250–280° (bath temperature) with 2 g. of 5% palladium–charcoal catalyst for 45 minutes. The mixture was diluted with methanol, filtered, evaporated and distilled to yield 16 g. of a colorless oil, b.p. 160° at 0.3 mm., $n^{25}D$ 1.5701.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02; CH_3O, 24.02. Found: C, 74.39; H, 7.18; CH_3O, 23.49.

(6) Details of the pharmacological studies will be reported elsewhere by Ivy and Gunter.

(7) Fieser and Hershberg, THIS JOURNAL, **58**, 2314 (1936).

(8) Hill, *ibid.*, **54**, 4105 (1932).

TABLE I

Hydroxy acid	Crystn. solvent, ml./g. crude	M.p., °C.	$FeCl_3$ test[a]
β-(1-Hydroxy-4-naphthoyl)-propionic	15 AcOH	235 (dec.)	Negative
γ-(1-Hydroxy-4-naphthoyl)-butyric	7 AcOH	203	Negative
δ-(1-Hydroxy-4-naphthoyl)-valeric	6 benzene[b]	163	Olive-green
ω-(1-Hydroxy-4-naphthoyl)-pelargonic	3 benzene	91–92	Purple
β-(1,5-Dihydroxy-4-naphthoyl)-propionic[c]	22 50% AcOH	175 (dec.)	Faint green
β-[1-Hydroxy-4-(5,6,7,8-tetrahydro)-naphthoyl]-propionic[d]	5 toluene[b]	186–187	Faint green
β-(2-Hydroxy-1-naphthoyl)-propionic[e]	10 toluene	116	Red
β-[2-Hydroxy-3-(5,6,7,8-tetrahydro)-naphthoyl]-propionic	6 toluene	143	Purple

[a] Tests conducted in alcoholic solution. [b] Purification effected by suspension in the indicated solvent at the boiling point. [c] Prepared by heating β-(1-hydroxy-5-methoxy-4-naphthoyl)-propionic acid (Hill, Short and Stromberg, *J. Chem. Soc.*, 937 (1937)) with two parts of aluminum chloride in seven volumes of chlorobenzene at 90–92° for one hour. [d] See Bachmann and Ness, THIS JOURNAL, **64**, 536 (1942), for parent methyl ether. [e] Obtained from β-(2-methoxy-1-naphthoyl)-propionic acid (Short, Stromberg and Wiles, *J. Chem. Soc.*, 320 (1936)).

Saponification produced an acid which, after two crystallizations from cyclohexane, melted at 91–92°. This melting point agrees quite well with that reported by Wahl[9] for γ-(2-methoxy-3-naphthyl)-butyric acid (m.p. 94°).

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; CH_3O, 12.7; CO_2H, 18.44. Found: C, 73.75; H, 6.61; CH_3O, 12.24; CO_2H, 18.17.

The product obtained by demethylation with hydriodic acid melted at 138–139° after crystallization from toluene. Wahl reported a melting point of 131° for γ-(2-hydroxy-3-naphthyl)-butyric acid.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.01; H, 6.11.

γ-Oxo-γ-(3-hydroxy-2-thianaphthene)-butyric Acid.[10]—Sixty-nine grams (0.52 mole) of aluminum chloride was added slowly at 0° to a stirred suspension of 40 g. (0.24 mole) of 3-methoxythianaphthene[11] and 26 g. (0.26 mole) of succinic anhydride in 250 ml. of *s*-tetrachloroethane. Stirring was continued for 2 hours at 0° after which the mixture was kept in the refrigerator for 3 days. Hydrolysis and steam distillation of the solvent gave a dark brown acid which was dissolved in 500 ml. of 10% sodium carbonate, the solution filtered through Celite and acidified. The crude product thus obtained (40 g.) was crystallized from 500 ml. of toluene and then from 400 ml. of ethyl acetate (Darco) to yield 16 g. of pale yellow needles, m.p. 190°. Since this compound contains no methoxyl group and gives an intense green ferric chloride test, it is evident that extensive demethylation occurred during the reaction.

Demethylation.—In several of the subsequent examples demethylation of the parent methoxy keto acids with hydrobromic or hydriodic acid in the conventional manner yielded intractable tars. The following procedure with minor modifications has been found applicable to a rather wide variety of types. The reaction proceeds smoothly, and yields are satisfactory, ranging from 75 to 90%. The constants of the compounds demethylated in this manner are summarized in Table I.

β-(1-Hydroxy-4-naphthoyl)-propionic Acid.—One hundred grams of aluminum chloride was added in several portions during a 5-minute period to a stirred suspension of 50 g. of β-(1-methoxy-4-naphthoyl)-propionic acid in 350 ml. of chlorobenzene. The mixture became homogeneous, and the temperature rose to about 40° with vigorous evolution of hydrogen chloride. After being heated and stirred at 60° (internal temperature) for 30 minutes, the hot, easily fluid reaction mixture was hydrolyzed with ice and hydrochloric acid, the solvent removed by steam distillation and the hot suspension of the crude acid filtered. Solution in an excess of hot 2% sodium hydroxide, treatment with Darco and acidification of the cooled filtrate yielded 44.8 g. of crude acid, m.p. 228° (dec.).

The methyl ester was prepared by refluxing a suspension of 72 g. of the above acid in 360 m. of methanol containing 18 ml. of sulfuric acid for 12 hours. Upon chilling a crop of greenish-yellow crystals was obtained, which was rinsed with cold methanol and recrystallized from 300 ml. of methanol (Darco) to give 47.5 g. of colorless needles melting at 151°.

γ-(1-Hydroxy-4-naphthyl)-butyric Acid.—A suspension of 19 g. of γ-(1-methoxy-4-naphthyl)-butyric acid[6] and 160 ml. of hydriodic acid (sp. gr. 1.66) was refluxed for 10 minutes. After dilution with ice-water the granular product was triturated with water, filtered and dried to give 17 g. of acid, m.p. 144–145°. Crystallization from 250 ml. of toluene yielded 15 g. of colorless crystals melting at 147–148°. An alcoholic solution gave a strong purple ferric chloride test.

β-(1-Hydroxy-4-naphthyl)-acrylic Acid.—A mixture of 25 g. of 1-hydroxy-4-naphthaldehyde, 25 g. of fused sodium acetate and 0.3 ml. of pyridine in 125 ml. of acetic anhydride was heated at 160–165° (bath temp.) under reflux for 9 hours. The cooled mixture was diluted with 500 ml. of water, heated at 60° with stirring for 30 minutes, chilled in an ice-bath and the supernatant liquor discarded. The tacky, yellow crude acid was dissolved in 125 ml. of hot alcohol, poured into two liters of 1% sodium hydroxide and filtered with Celite. Saturation of the filtrate with carbon dioxide precipitated 8 g. of unreacted aldehyde. Acidification of the filtrate yielded 6 g. of yellow acid which did not melt but decomposed at 132–133°. Crystallization from a variety of solvents was unsatisfactory. An alcoholic solution of the acid gave a strong red color with ferric chloride. Attempts to prepare this acid from 1-hydroxy-4-naphthaldehyde and malonic acid under various conditions were unsuccessful.

β-(1-Hydroxy-2(?)-bromo-4-naphthoyl)-propionic Acid.—This acid was obtained as the principal product in an unsuccessful attempt to prepare β-(1-hydroxy-4-naphthoyl)-acrylic acid.

A solution of 32 g. (0.2 mole) of bromine in 100 ml. of acetic acid was added dropwise during a 40-minute period at 60° to a stirred suspension of 48.8 g. (0.2 mole) of β-(1-hydroxy-4-naphthoyl)-propionic acid in 488 ml. of acetic acid. The dark solution was cooled to 25° and stirred for 30 minutes, after which the solvent was distilled under reduced pressure. The partially crystalline residue was suspended in 200 ml. of benzene, stored overnight, filtered, rinsed with a little benzene and dried in vacuum over alkali. The slate colored product weighed 32 g.

A stirred solution of the crude acid and 10.6 g. of fused sodium acetate in 106 ml. of acetic acid was refluxed for 30 minutes. The reactants soon dissolved, followed immediately by the precipitation of sodium bromide. The solvent was removed under reduced pressure, the residue diluted with water and the granular, yellow acid filtered. Two crystallizations from acetic acid followed by one from ethanol yielded 10.8 g. of bright yellow crystals melting at 189–190° with decomposition. The possibility of this material being a β-ketoacrylic acid was eliminated by demonstrating its stability in hot alcoholic potassium hydroxide solution.

1-Naphthyl Crotonate.—A lukewarm solution of 95 g. (0.66 mole) of 1-naphthol in 250 ml. of benzene was added in several portions to a stirred solution of 69.7 g. (0.66 mole) of crotonyl chloride and 64 g. of anhydrous pyridine in 250 ml. of benzene. After the initial reaction had subsided, the stirred mixture was refluxed for 5 hours, cooled, diluted with 500 ml. of ether, washed thoroughly with dilute hydrochloric acid, then with dilute alkali and finally with water. Removal of solvent and distillation yielded 48 g. of a pale yellow oil, b.p. 144–149° at 0.6 mm., $n^{25}D$ 1.5989. It

(9) Wahl, *Compt. rend.*, **206**, 683 (1938).

(10) This experiment was conducted by Mr. Harry Arbit.

(11) Methylation of 3-hydroxythianaphthene with methyl sulfate was unsuccessful, but the reaction was readily effected with diazomethane in 70% yield.

TABLE II

	Empirical formula	Analyses, % Calcd. C	Calcd. H	Obsd. C	Obsd. H	Choleretic activity Molar basis	Choleretic activity Weight basis
β-(1-Methoxy-4-naphthoyl)-propionic acid						115	179
β-(1-Hydroxy-4-naphthoyl)-propionic acid	$C_{14}H_{12}O_4$	68.8	4.95	68.6	5.05	78	129
Methyl β-(1-hydroxy-4-naphthoyl)-propionate	$C_{15}H_{14}O_4$	69.8	5.46	70.1	5.85	46	72
γ-(1-Hydroxy-4-naphthyl)-butyric acid	$C_{14}H_{14}O_3$	73.0	6.13	73.2	5.90	49	86
γ-(1-Hydroxy-4-naphthyl)-butyric acid diethylamide	$C_{18}H_{23}O_2N$	4.91[a]		4.92		15	19
γ-(1-Hydroxy-4-naphthoyl)-butyric acid	$C_{15}H_{14}O_4$	69.8	5.46	69.6	5.44	36	56
δ-(1-Hydroxy-4-naphthoyl)-valeric acid	$C_{16}H_{16}O_4$	70.6	5.92	70.2	6.10	50	74
ω-(1-Hydroxy-4-naphthoyl)-pelargonic acid	$C_{20}H_{24}O_4$	73.1	7.36	72.2	7.44	24	29
β-(1-Hydroxy-2-naphthoyl)-propionic acid	$C_{14}H_{12}O_4$	68.8	4.95	68.7	5.01	91	150
β-(1-Methoxy-4-naphthoyl)-acrylic acid[b]	$C_{15}H_{12}O_4$	70.3	4.72	70.1	4.68	111	186
β-[1-Hydroxy-4-(5,6,7,8-tetrahydro)-naphthoyl]-propionic acid	$C_{14}H_{16}O_4$	67.7	6.50	67.6	6.57	82	133
β-(1-Hydroxy-5-methoxy-4-naphthoyl)-propionic acid[c]						46	67
β-(1,5-Dihydroxy-4-naphthoyl)-propionic acid	$C_{14}H_{12}O_5$	64.6	4.65	64.8	4.90	43	66
β-(1-Hydroxy-2(?)-bromo-4-naphthoyl)-propionic acid	$C_{14}H_{11}O_4Br$	52.0	3.40	52.2	3.36	74	92
β-(1-Hydroxy-4-naphthyl)-acrylic acid	$C_{13}H_{10}O_3$	72.9	4.71	72.6	5.10	44	83
1-Hydroxy-4-naphthoic acid[d]						6	13
β-(2-Hydroxy-1-naphthoyl)-propionic acid	$C_{14}H_{12}O_4$	68.8	4.95	68.8	4.94	52	86
β-(2-Hydroxy-3-naphthoyl)-propionic acid[e]						52	86
β-(2-Hydroxy-6-naphthoyl)-propionic acid[f]						93	153
β-[2-Hydroxy-3-(5,6,7,8-tetrahydro)-naphthoyl]-propionic acid	$C_{14}H_{16}O_4$	67.7	6.50	67.9	6.48	90	146
γ-Oxo-γ-(3-hydroxy-2-thianaphthene)-butyric acid	$C_{12}H_{10}O_4S$	57.6	4.03	57.6	4.03	35	55
2-Butyryl-1-naphthol[g]						14	26
4-Butyryl-1-naphthol[g]						41	77
4-Crotonyl-1-naphthol	$C_{14}H_{12}O_2$	79.2	5.70	79.2	5.82	75	142

[a] Nitrogen analysis. [b] Dave, Bokil and Nargund, *J. Univ. Bombay*, **10**, Pt. 3, 122 (1941), reported m.p. 192°. Our product melted at 207° (dec.) after repeated crystallization from ethyl acetate. [c] Hill, Short and Stromberg, *loc. cit.* [d] Heller, *Ber.*, **45**, 674 (1912). [e] Wahl, *loc. cit.* [f] Obtained by hydriodic acid demethylation of the parent methoxy derivative which was prepared according to Short, Stromberg and Wiles, *loc. cit.* See Robinson and Thompson, *J. Chem. Soc.*, 2009 (1938). [g] Stoughton, THIS JOURNAL, **57**, 202 (1935).

became crystalline on standing in the refrigerator, m.p. about 27°.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.4; H, 5.73.

4-Crotonyl-1-naphthol.—Forty-one grams (0.3 mole) of aluminum chloride was added portionwise at 2–4° to a stirred solution of 48 g. (0.22 mole) of 1-naphthyl crotonate in 200 ml. of nitrobenzene. The mixture was stirred for 19 hours at 8–10°, hydrolyzed and the solvent steam distilled. Solution of the residual red oil in two liters of 2% sodium hydroxide at *laboratory temperature*, filtration with Celite and acidification of the filtrate gave a red oil which soon became crystalline. The dried acid (21.3 g.) was crystallized from 100 ml. of benzene (Darco), yielding 15 g. of almost colorless product, m.p. 124–125°. A solution in alcohol gave no coloration with ferric chloride. Treatment with diazomethane and hypochlorite oxidation of the resulting methyl ether gave the known 1-methoxy-4-naphthoic acid.

β-(1-Acetoxy-2-naphthoyl)-propionic Acid.—A stirred suspension of 186 g. (1.0 mole) of 1-acetoxynaphthalene and 110 g. (1.1 moles) of succinic anhydride in one liter of nitrobenzene was treated portionwise at 3–5° with 293 g. (2.2 moles) of aluminum chloride. The mixture was stirred for 2 hours longer at 5° and then allowed to stand at laboratory temperature overnight. After hydrolysis and steam distillation of the solvent, the residue was chilled and filtered. The crude product was suspended in 2.5 liters of 5% sodium carbonate, filtered with Darco and the filtrate chilled. The crystalline precipitate, which was a mixture of acetylnaphthols, was filtered and the filtrate saturated with carbon dioxide. After 1 hour the mixture was filtered to remove a second crop of acetylnaphthols. Acidification of the filtrate gave 46 g. of crude acid, m.p. 145–160°, which was hydrolyzed without further treatment. A sample for analysis was crystallized from methyl ethyl ketone, m.p. 183–184°.

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 67.14; H, 5.16.

β-(1-Hydroxy-2-naphthoyl)-propionic Acid.—A solution of 39 g. of the crude acetoxy derivative in 195 ml. of alcohol and 195 ml. of hydrochloric acid (sp. gr. 1.19) was refluxed for 10 minutes and diluted with 1.5 liters of water. The waxy, gray acid thus obtained (39 g.) was crystallized from 320 ml. of isopropyl alcohol (Darco) to yield 24 g. of yellow crystals melting at 104–106°. Repeated crystallization from isopropyl alcohol raised the melting point to 106–108°.

γ-(1-Hydroxy-4-naphthyl)-butyric Acid Diethylamide.—A solution of 50.6 g. (0.22 mole) of γ-(1-hydroxy-4-naphthyl)-butyric acid in 102 ml. of pyridine was treated in several portions with 68 ml. (0.66 mole) of acetic anhydride. After 24 hours the solvent was distilled under reduced pressure, the viscous residue suspended in 300 ml. of water containing 25 ml. of hydrochloric acid and the mixture stored overnight in the refrigerator. The crude product was triturated with 3% hydrochloric acid, rinsed well with water and dried. Three crystallizations from ten volumes of benzene yielded 17.5 g. of γ-(1-acetoxy-4-naphthyl)-butyric acid melting at 132–134°.

A mixture of 15 g. of the above acid and 9 ml. of thionyl chloride in 45 ml. of carbon tetrachloride was refluxed for 2 hours. After removal of solvent under vacuum at 100° the acid chloride thus obtained was dissolved in 25 ml. of benzene and treated portionwise with a solution of 11.5 g. of diethylamine in 25 ml. of benzene. The resulting gelatinous mixture was refluxed for 3 hours, poured into an excess of 2% hydrochloric acid, extracted with ether and the ether extract washed successively with 5% sodium carbonate and water. The crude diethylamide (15 g.) obtained by distillation of the solvent was deacetylated without further treatment.

The amide was dissolved in 65 ml. of methanol, 8.5 ml. of concentrated hydrochloric acid added with shaking and the solution stored at laboratory temperature for 3 days. Removal of one-half of the solvent under reduced pressure and dilution of the residue with ice-water gave the granular, crude product (13.5 g.). Two crystallizations from ten volumes of toluene with Darco yielded 9.5 g. of the desired diethylamide, m.p. 155–156°.

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