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Gadsby et al.

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[54] **THIO DERIVATIVES OF 2-HYDROXY-3-NAPHTHIOC ACID**

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[52] **U.S. Cl.**.....**260/516,** 260/247.1, 260/251 A, 260/294.8 B, 260/302 R, 260/326.3, 260/470, 260/473 S, 260/501.21, 260/543 H, 260/609 D, 424/248, 424/251, 424/263, 424/270, 424/274, 424/308, 424/309, 424/317, 424/319

[51] **Int. Cl.**.....**C07c 149/40**

[58] **Field of Search**.....260/470, 516, 302, 294.8

[56] **References Cited**

FOREIGN PATENTS OR APPLICATIONS

706,659 4/1941 Germany.....280/516

OTHER PUBLICATIONS

Whitmore et al., Chem. Abst. 61, 7151 (1964)

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[57] **ABSTRACT**

Fibrinolytic agents related to 1-thio- and 1-thiomethyl-2-hydroxy-3-naphthoic acid.

17 Claims, No Drawings

THIO DERIVATIVES OF 2-HYDROXY-3-NAPHTHIOC ACID

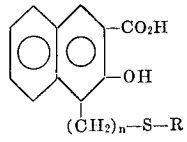
BACKGROUND OF THE INVENTION

This invention relates to naphthoic acids, and more particularly to a series of 1-thio- and 1-thiomethyl-2-hydroxy-3-naphthoic acids and the basic salts and lower alkyl esters thereof, useful as fibrinolytic agents.

British Pat. No. 1,007,021, published Oct. 13, 1965, discloses 4,4'-thiobis(3-hydroxy-2-naphthoic acid), reported useful as salts of 1-aryl-1,2-dihydro-4,6-diamino-s-triazines, and 2-hydroxy-6-methylthio-3-naphthoic acid is reported, German Pat. No. 548,823, to be useful as a dyestuff intermediate. Barber, U.S. Pat. No. 2,641,610, and Elslager, et al., U.S. Pat. No. 2,731,470 report 1,1-methylenebis(2-hydroxy-3-naphthoic acid) useful as a derivatizing salt in pharmaceutical preparation.

SUMMARY OF THE INVENTION

The fibrinolytic agents of the present invention are represented by the formula:



and the basic salts and lower alkyl esters thereof, wherein:

R is selected from the group consisting of alkyl and cycloalkyl each containing from three to 10 carbon atoms; phenyl, benzyl and mono- and disubstituted phenyl and benzyl said substituent being selected from the group consisting of fluorine, chlorine, bromine, hydroxy, alkyl and alkoxy each containing from one to four carbon atoms, trifluoromethyl, nitro and amino and substituted amino said substituent being selected from the group consisting of alkyl and acyl each containing from one to four carbon atoms, dialkyl each containing from one to four carbon atoms and phenylsulfonyl; naphthyl; pyridyl and thiazolyl; and

n is an integer of 0 or 1.

As has been previously noted, a characteristic feature of the acidic compounds of the instant invention is their ability to form basic metal salts. Acid congeners of the present invention are converted to basic salts by the interaction of said acid with an appropriate base in an aqueous or non-aqueous medium. Such basic reagents suitably employed in the preparation of said salts can vary in nature, and are meant to contemplate such bases as organic amines, ammonia, alkali metal hydroxides, carbonates, bicarbonates, hydrides and alkoxides, as well as alkali earth metal hydroxides, hydrides, alkoxides and carbonates. Representative of such bases are ammonia, primary amines such as n-propylamine, n-butylamine, aniline, cyclohexylamine, benzylamine, p-toluidine, ethylamine, octylamine, tertiary amines such as diethylaniline, N-methyl-pyrrolidine, N-methylmorpholine and 1,5-diazabicyclo-[4,3,0]-5-nonene; sodium hydroxide, potassium hydroxide, ammonium hydroxide, sodium ethoxide, potassium methoxide, magnesium hydroxide, calcium hydride and barium hydroxide.

In a similar manner, treatment of the basic salts with an aqueous acid solution, e.g., mono-, di- or tribasic acid results in the regeneration of the free acid form. Such conversions are best carried out as rapidly as possible and under temperature conditions and method dictated by the stability of said acid products. The acids thus generated can be reconverted to the same or a different basic salt.

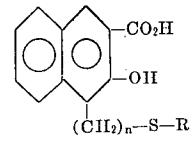
In the utilization of the chemotherapeutic activity of those compounds of the present invention which form basic salts, it is preferred, of course, to use pharmaceutically acceptable salts. Although water-insolubility, high toxicity, or lack of crystalline nature may make some salt species unsuitable or less desirable for use as such in a given pharmaceutical application, the water insoluble or toxic salts can be converted to the corresponding acids by decomposition of the salts as described above, or alternately they can be converted to any desired pharmaceutically acceptable basic salt. The said pharmaceutically acceptable salts preferred are those wherein the cation is ammonium, sodium or potassium.

The term lower alkyl encompasses those alkyl groups containing one to four carbon atoms.

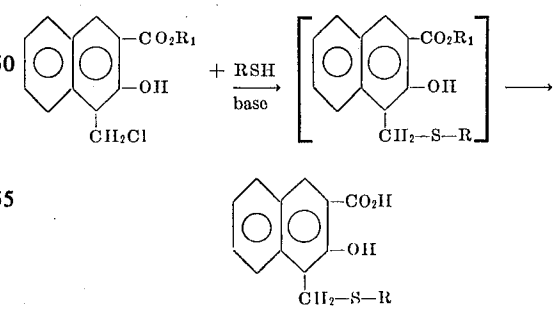
Of particular interest, because of their fibrinolytic activity, are compounds where R is mono- and disubstituted phenyl or branched alkyl containing three to 10 carbon atoms and *n* is an integer of 0 or DESCRIPTION 1.

DETAILED DESCRO OF THE INVENTION

In accordance with the process employed for preparing the 1-thio- and 1-thiomethyl-2-hydroxy-3-naphthoic acids of the present invention of the formula:



wherein R is as previously indicated, *n* is 1 and R_1 is alkyl containing from one to four carbon atoms, the following scheme is illustrative:



I

A lower alkyl ester of 1-chloromethyl-2-hydroxy-3-naphthoic acid in a reaction-inert solvent such as ethanol or methanol is contacted with at least an equimolar amount of a mercaptan of the formula RSH, in the presence of a base, e.g., sodium and potassium (lower) alkoxides or carbonates. It is preferred that at least two equivalents of said base be employed.

The aforedescribed reaction is carried out at a reaction temperature of 40° C. to the reflux temperature of the selected solvent for a reaction time of 12 to 24 hours; reflux temperatures are preferred.

A convenient method of isolation employs cooling, filtration of the alkali metal chloride and evaporation of the reaction mixture filtrate to dryness, followed by dissolution of the residue in water and subsequent acidification of the aqueous solution. The precipitated acid is filtered and further purified by recrystallization from a suitable solvent.

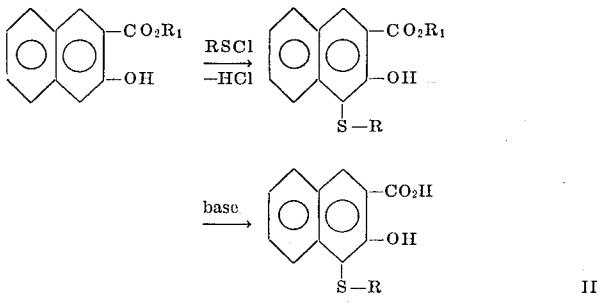
Also within the purview of this invention are the esters of final products. These intermediate products are isolated by reducing the amount of base in the aforedescribed reaction such that only one equivalent is employed. Said esters are isolated, after filtration of the alkali metal chloride, by evaporation of the filtrate to dryness and recrystallization of the residue from a suitable solvent.

Alternately, the esters can be formed from the acids by the conventional Fischer esterification methods well known to those skilled in the art.

The requisite mercaptans, RSH, are either available commercially or can easily be prepared by one skilled in the art by the methods of Newman, et al., J. Org. Chem., 31, 3980 (1966), Kipnis, et al., J. A. C. S., 71, 2270 (1949) and those outlined by Wagner, et al., "Synthetic Organic Chemistry," John Wiley & Sons, Inc., New York, 1953, Chapter 31, page 778.

The lower alkyl esters of 1-chloromethyl-2-hydroxy-3-naphthoic acid are prepared via chloromethylation of the corresponding 2-hydroxy-3-naphthoate esters by the procedures as taught by Tarbell, et al., J. Am. Chem. Soc., 76, 5766 (1954).

Compounds of the present invention wherein R is as previously described, *n* is an integer of 0 and R_1 is alkyl containing from one to four carbon atoms, are synthesized by the reactions outlined as follows:



II

The reaction leading to compounds of formula II employs contacting a lower alkyl ester of 2-hydroxy-3-naphthoic acid with a sulfenyl chloride, R–S–Cl, in a reaction-inert solvent such as chloroform, carbon tetrachloride, benzene or toluene.

In practice, a solution of the naphthoate ester is treated with at least an equimolar amount of the requisite sulfenyl chloride plus as much as a 50 percent excess. Reaction times are not critical and vary with reaction temperature, concentration and reactivity of the respective reactants. In general, reaction times of 24–48 hours are operative, with corresponding reaction temperatures of 15° C. up to the reflux temperature of the solvent employed.

Evaporation of the reaction solvent followed by recrystallization of the residual solid leads to the isolation of the purified esters of formula II, which are also considered within the scope of this invention.

Subsequent hydrolysis of the esters of formula II to yield the products of the instant invention is carried out in a manner familiar to those skilled in the art and comprises treating II in an inert solvent such as ethanol or water with at least an equimolar amount of base such as sodium hydroxide, potassium hydroxide or sodium carbonate, at temperatures of 60°–100° C. for 12 to 20 hours.

When ethanol is the employed solvent, the aforedescribed reaction is cooled, filtered and the ethanol removed in vacuo. The residual solid is dissolved in a minimum amount of water and the product precipitated by the addition of 2N hydrochloric acid. Filtration and recrystallization leads to the pure products of the present invention.

The requisite sulfenyl chlorides employed in the aforedescribed reaction are either commercially available or can be prepared from the corresponding mercaptan by one skilled in the art according to literature procedure, such as those taught by Reid, "Organic Chemistry of Bivalent Sulphur," Chemical Publishing Co., Inc., New York, 1958, Volume I, Chapter 3, page 262.

Compounds of the instant invention wherein R is derived from a nitrophenyl or nitrobenzyl moiety can be further transformed through reduction to the corresponding amino congeners. Said reduction is most conveniently carried out using stannous chloride and hydrochloric acid at temperatures of 40°–75° C. for reaction periods of 2 to 4 hours. After the reaction is complete it is made strongly basic with ammonium hydroxide, the stannic hydroxide filtered and the product isolated from the basic filtrate by adjusting the pH to the isoelectric point with an acid such as acetic acid.

Amines resulting from the aforedescribed reduction of the corresponding nitro compounds can subsequently be reacted with a wide variety of reagents including alkanoyl halides, anhydrides, sulfonyl halides and alkyl halides.

Reaction of said amino compounds with alkanoyl halides leads to the preparation of the corresponding acylamino analogs. In practice, the alkanoyl halide, preferably the chloride, is added slowly to the requisite amino compound in a solvent such as pyridine. Reaction temperatures of from 60°–85° C. are employed with reaction times of 3 to 6 hours. The solvent is removed under reduced pressure and the residual pyridium salt of the product converted to the free acid by treating an aqueous solution thereof with sufficient acid to precipitate the product.

Analogously, sulfonyl halides are reacted under similar conditions and give rise to the corresponding sulfonamides.

Formation of acylamino analogs employing simple or mixed anhydrides in place of the alkanoyl halides can be carried out with equal ease. Experimentally, the amino compound is contacted with at least an equimolar amount of the requisite anhydride plus as much as a 20–50 percent excess. A solvent such as benzene, chloroform or tetrahydrofuran can be employed or the reaction can be run neat, i.e., without sol-

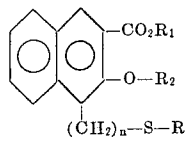
vent. Said reaction is carried out at 40°–80° C. for 2–8 hours. The desired product is isolated by removal of the excess anhydride and solvent in vacuo.

Alkylation of the amine moiety is carried out using an appropriate alkyl halide, preferably iodide. The extent of alkylation is controlled by the relative amount of alkyl halide to the amino compound employed. For mono alkylation equimolar quantities of the two reactants are used plus a small, 10 percent, excess of the alkyl halide, dialkylation requires at least 2 moles of halide per mole of amino substrate for optimum yields. In practice, a suspension or solution of the amino compound and at least 2 moles of an alkali metal carbonate is treated with the appropriate alkyl halide in the amounts previously described. The solvents for this alkylation can vary in nature and are selected from the group including (lower)alkanols, N,N-di(lower)alkyl(lower)alkylcarboxamides, cyclic ethers and water. Elevated temperatures of from 50°–110° C. are employed, with reaction times of 1–8 hours. The product is isolated by dilution with water followed by adjustment of the pH with acid to the isoelectric point, generally just acid to Congo red paper. Cooling and seeding facilitates crystallization.

As previously indicated, the 1-thio- and 1-thiomethyl-2-hydroxy-3-naphthoic acids and lower alkyl esters thereof of the present invention are all readily adapted to therapeutic use as fibrinolytic agents. Typical member compounds of interest in this series include 1-(o-isopropylphenylthiomethyl)-2-hydroxy-3-naphthoic acid, 1-(o-bromophenylthiomethyl)-2-hydroxy-3-naphthoic acid, 1-(1,1,3,3-tetramethyl-n-butylthiomethyl)-2-hydroxy-3-naphthoic acid, 1-(o-chlorophenylthiomethyl)-2-hydroxy-3-naphthoic acid, 1-(p-chlorophenylthiomethyl)-2-hydroxy-3-naphthoic acid, 1-(p-chlorophenylthio)-2-hydroxy-3-naphthoic acid, 1-(o-tolylthiomethyl)-2-hydroxy-3-naphthoic acid, 1-(m-tolylthiomethyl)-2-hydroxy-3-naphthoic acid, 1-(p-tolylthiomethyl)-2-hydroxy-3-naphthoic acid, 1-(o-bromophenylthiomethyl)-2-hydroxy-3-naphthoic acid, 1-(m-bromophenylthiomethyl)-2-hydroxy-3-naphthoic acid and 1-(2,3-dichlorophenylthiomethyl)-2-hydroxy-3-naphthoic acid.

As previously mentioned, the corresponding esters of the compounds of the instant invention are also valuable fibrinolytic agents and are hydrolyzed in vivo to the corresponding acids. Further, said esters are valuable intermediates leading to the synthesis of the subject compounds.

Also considered within the scope of the present invention are compounds of the formula:



where R_1, n and R are as previously described and R_2 is alkanoyl containing one to four carbon atoms. Said acylated products are conveniently prepared by acylation of the phenolic hydroxyl group. In practice, the phenolic compound is contacted with at least an equimolar amount of an anhydride or acid halide, preferably chloride, in a reaction-inert solvent such as chloroform, benzene or tetrahydrofuran. Reaction temperatures of 50°–80° C. are employed with reaction periods of 1–4 hours. When an acid halide is used as the acylating agent it is desirable to use in addition at least an equivalent of a tertiary amine such as pyridine or triethylamine. The products are isolated by evaporation of the reaction mixture to dryness followed by trituration with water, filtration and drying.

The terminal complication of thrombus formation in ischaemic heart disease, cerebral vascular disease, leg-vein thrombosis, pulmonary embolism and peripheral vascular disease is well documented in the medical literature, and has recently been reviewed by Poole, et al., J. Atheroscler. Res., 1, 251–282 (1961).

One approach to the problem of thrombi formation is to enhance the rate of dissolution of the fibrin, a major constituent of both clots and thrombi. It is through this mechanism that the compounds of the present invention mediate their remarkable fibrinolytic activity.

The activity of compounds of the invention as fibrinolytic agents is assessed in vitro as their ability to facilitate:

1. the visible lysis of clots formed on addition of thrombin and calcium chloride to human blood plasma:

2. the release of fluorescein from clots formed on the addition of thrombin to human blood plasma containing fluorescein-labelled fibrinogen; or

3. the release of erythrocytes, by potentiation of urokinase-induced lysis, from clots formed on addition of thrombin and urokinase to freshly withdrawn human or animal blood samples.

In test (1), the test compound, dissolved in neutral buffer, is mixed with human plasma to provide concentrations of 2.5, 1.0 and 0.25 mM; clotting is initiated by addition of $CaCl_2$ and thrombin. The clots are then removed and immersed in solutions of the test compound in buffer, at the same concentrations as in the plasma mixtures. The clots are inspected for lysis after incubation for 24 and 48 hours at 37° C.

In test (2), human plasma (2 vols) is mixed with 0.5 percent fluorescein labelled fibrinogen (1 vol). Clots are prepared by adding thrombin (0.1 ml., 0.1 mg/ml.) to 0.2 ml. of the mixture. The clots are washed with neutral buffer, and are then incubated in a mixture containing 0.3 ml. of human serum, 0.1 ml. of 0.5 M Na Cl, 0.8 ml. of the test compound (1, 2, 3, 4 and 5 mM) in tris(hydroxymethyl)methylamine/HCl buffer, pH 7.4. The fluorescence of the supernatant fluid is measured at 0 and 16 hours.

In test (3), into ice-cold test-tubes are pipetted various concentrations of the test compound, urokinase (10 units per clot for human blood and 200–250 units per clot for rat blood), and thrombin (2 units) all in a final volume of 0.2 ml. Freshly drawn blood is quickly chilled and a 0.3 ml. aliquot is pipetted into each tube. The clots are incubated for 1 hour at 37° C., and then filtered through cotton wool and washed with saline. Filtrate and washings are combined, made to a standard volume, and the erythrocytes lysed with Triton X 100. Determination of the hemoglobin at 540 mμ provides a measure of fibrinolysis.

Activity in vivo is also assessed by method (3), by administering the compounds, orally or parenterally, e.g.,

intravenously, to experimental animals before withdrawing the blood samples, instead of including them in the test medium.

The 1-thio- and 1-thiomethyl-2-hydroxy-3-naphthoic acids and the pharmaceutically acceptable salts and lower alkyl esters thereof, which are useful as fibrinolytic agents, may be administered either as individual therapeutic agents or as mixtures of therapeutic agents. They may be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets or capsules containing such excipients as starch, milk sugar or certain types of clay, etc. They may be administered orally in the form of elixirs or oral suspensions with the active ingredients combined with emulsifying and/or suspending agents. They may be injected parenterally, and for this use they, or appropriate derivatives, may be prepared in the form of sterile aqueous solutions. Such aqueous solutions should be suitably buffered, if necessary, and should contain other solutes such as saline or glucose to render them isotonic.

The dosage required to prevent thrombus formation in subjects prone to said disorder would be determined by the severity of the symptoms and is within the skill of the art. Generally, small doses will be administered initially, with a gradual increase in the dosage until the optimum level is determined. It will generally be found that when the composition is administered orally, larger quantities of the active ingredient will be required to produce the same level as produced by a small quantity administered parenterally. In general, from about 10 to about 200 mg. of active ingredient per kilogram of body weight are administered in single or multiple dose units, to effectively facilitate thrombus dissolution.

The following examples are provided solely for the purpose of illustration and are not to be construed as limitations of this invention, many variations of which are possible without departing from the spirit or scope thereof.

EXAMPLE I

1-(o-Isopropylphenylthiomethyl)-2-hydroxy-3-naphthoic Acid and Ethyl Ester

A. A mixture of 7.5 g. of methyl 1-chloromethyl-2-hydroxy-3-naphthoate, 4.6 g. of o-isopropylbenzenethiol and 4.2 g. of potassium carbonate in 160 ml. of ethanol is heated to reflux for 18 hours. The reaction mixture is cooled, filtered and evaporated to dryness. The residual solid is dissolved in water, the crude product precipitated by the addition of 2N hydrochloric acid and solids filtered and recrystallized from ethanol, 6.3 g., m.p. 192°–193° C.

Anal. Calcd. for $C_{21}H_{20}O_3S$: C, 71.55; H, 5.72.
Found: C, 71.74; H, 5.56.

B. The above acid is suspended in 50 ml. of dry ethanol and heated to reflux while hydrogen chloride gas is slowly bubbled into solution. After 30 minutes the addition of gas is terminated and the solution allowed to reflux for an additional hour. The excess gas and solvent are removed in vacuo and the residue recrystallized from chloroform.

EXAMPLE II

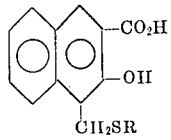
Starting with methyl 1-chloromethyl-2-hydroxy-3-naphthoate and the appropriate mercaptan, and following the procedure of Example I, the following congeners are prepared:

1-(o-Tolylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 202°–204° C.;
1-(m-Tolylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 193°–195° C.;
1-(p-Tolylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 205°–207° C.;
1-Phenylthiomethyl-2-hydroxy-3-naphthoic acid, m.p. 216°–219° C.;
1-Benzylthiomethyl-2-hydroxy-3-naphthoic acid, m.p. 193°–195° C.;
1-(2-Naphthylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 212°–214° C.;
1-(p-chlorophenylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 229°–230° C.;
1-(o-chlorphenylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 228°–229° C.;
1-(2,3-Dichlorophenylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 255°–257° C.;
1-(o-Bromophenylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 237°–240° C.;
1-(p-Bromophenylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 221°–224° C.;
1-(m-Bromophenylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 220°–222° C.;
1-(p-Fluorophenylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 199°–201° C.;
1-(m-Trifluoromethylphenylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 228°–231° C.;
1-(o-Methoxyphenylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 208°–210° C.;
1-(m-Methoxyphenylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 182°–184° C.;
1-(p-Methoxyphenylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 211°–213° C.;
1-(p-Hydroxyphenylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 226°–228° C.;
1-(p-Nitrophenylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 256°–257° C.;
1-(p-Acetamidophenylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 240°–242° C.;
1-(p-t-Butylphenylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 195°–197° C.;
1-(3,5-Dimethylphenylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 222°–224° C.;
1-(2-Pyridylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 248°–250° C.;
1-Isobutylthiomethyl-2-hydroxy-3-naphthoic acid, m.p. 152°–153° C.;
1-(t-Butylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 247°–250° C.;
1-(1,1,3,3-Tetramethylbutylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 160°–162° C.;
1-(n-Decylthiomethyl)-2-hydroxy-3-naphthoic acid, m.p. 125°–127° C.;
1-Cyclohexylthiomethyl-2-hydroxy-3-naphthoic acid, m.p. 175°–177° C.

along with their methyl esters.

EXAMPLE III

The procedure of Example I is repeated, employing the requisite mercaptan, to provide the following analogs:

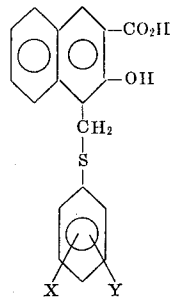


R	R
n-propyl	n-nonyl
i-propyl	cyclopropyl
n-butyl	cyclobutyl
s-butyl	cyclopentyl
n-pentyl	3-methylcyclopentyl
2-methyl-n-butyl	cyclohexyl
3-methyl-n-butyl	4,4-dimethylcyclohexyl
n-hexyl	4-ethylcyclohexyl
2-methyl-n-pentyl	cycloheptyl
4-methyl-n-pentyl	4,5-dimethylcycloheptyl
4,4-dimethyl-n-butyl	cyclooctyl
n-heptyl	cyclononyl
4,4-dimethyl-n-pentyl	cyclodecyl
2,2,3-trimethyl-n-butyl	
n-octyl	
3,4,4-trimethyl-n-pentyl	
2,2,3,3-tetramethyl-n-pentyl	

and their n-propyl esters.

EXAMPLE IV

The experimental procedure of Example I is repeated, starting with the appropriately substituted thiophenol, to provide the following compounds:

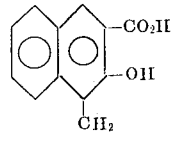


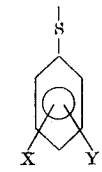
X	Y	X	Y
3-Cl	H	2-F	6-F
2-Cl	4-Cl	2-Cl	5-CF_3
2-Cl	6-Cl	2-Br	5-CF_3
3-Cl	4-Cl	2-F	5-CF_3
3-Cl	5-Cl	4-CF_3	H
2-Br	3-Br	3-Cl	5-CF_3
2-Cl	4-Br	2-F	3-F
2-Br	4-Br	2-Br	6-Br
3-Cl	5-Br	2-F	H
3-F	H	2-F	4-F
2-F	4-Cl	3-F	5-F

and their ethyl esters.

EXAMPLE V

The procedure of Example I is again repeated, starting with the requisitely substituted thiophenol, to prepare the following congeners:



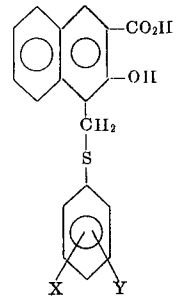


X	Y	X	Y
2-ethyl	H	2-methoxy	4-methyl
4-ethyl	H	2-methoxy	4-hydroxy
2-methyl	6-methyl	2-hydroxy	H
2-ethyl	6-ethyl	3-hydroxy	H
2-n-propyl	H	3-hydroxy	4-hydroxy
2-methyl	4-methyl	2-hydroxy	4-hydroxy
2-methyl	4-ethyl	2-methyl	4-hydroxy
2-methyl	4t-butyl	2-hydroxy	4-methyl
2-i-propyl	4-methyl	2-ethoxy	4-hydroxy
4-i-butyl	H	3-hydroxy	4-n-propyl
3-n-propyl	5-n-propyl	2-methyl	4-n-butoxy
2-methyl	4-methoxy	2-methyl	4-t-butyl
2-methyl	3-ethoxy	4-i-butoxy	H
2-methoxy	6-methoxy	2-methyl	4-chloro
2-ethoxy	H	2-methyl	4-bromo
4-n-butoxy	H	2-methyl	4-fluoro
4-i-propoxy	H	2-chloro	4-ethyl
2-bromo	4-t-butyl	3-trifluoromethyl	4-methyl
3-chloro	5-n-propyl	3-trifluoromethyl	6-methyl
2-fluoro	4-methyl	3-trifluoromethyl	5-ethyl
4-fluoro	2-i-propyl	2-methyl	3-- - - - - - - - - - aut-oromethyl
4-chloro	2-i-propyl	2-i-propyl	4-chloro
2-bromo	4-ethoxy	2-i-propyl	3-chloro
2-bromo	4-n-propoxy	2-bromo	3- - methoxy
2-bromo	4-hydroxy	2-hydroxy	4-chloro

and their n-butyl esters.

EXAMPLE VI

Starting with methyl 1-chloromethyl-2-hydroxy-3-naphthoate and the appropriate thiophenol and employing the experimental procedure of Example I, the following analogs are synthesized:



X	Y	X	Y
2-nitro	H	2-nitro	4-methoxy
3-nitro	H	2-nitro	4-hydroxy
2-nitro	4-methyl	3-nitro	5-trifluoromethyl
2-nitro	3-ethyl	3-nitro	6-methoxy
2-nitro	4-chloro	3-nitro	4-n-butoxy
3-nitro	2-ethyl	4-nitro	2-hydroxy
3-nitro	6-methyl	4-nitro	2-i-propoxy
3-nitro	6-i-propyl	4-nitro	2-ethoxy
3-nitro	5-n-butyl	4-nitro	2-fluoro
3-nitro	4-bromo	3-nitro	5-s-butyl
3-nitro	4-chloro	3-nitro	5-hydroxy
4-nitro	2-chloro	3-nitro	4-fluoro
4-nitro	3-chloro	2-nitro	6-methyl

4-nitro	2-i-propyl	2-nitro	6-bromo
4-nitro	2-bromo	2-nitro	4-fluoro
4-nitro	2-n-butyl	2-nitro	4-t-butyl

EXAMPLE VII

The procedure of Example I is repeated again, starting with the appropriate mercaptan, to provide the following analogs:

1-(1-Naphthylthiomethyl)-2-hydroxy-3-naphthoic acid;

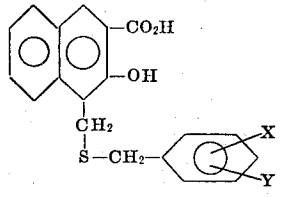
1-(3-Pyridylthiomethyl)-2-hydroxy-3-naphthoic acid;

1-(4-Pyridylthiomethyl)-2-hydroxy-3-naphthoic acid;

1-(2-Thiazolylthiomethyl)-2-hydroxy-3-naphthoic acid.

EXAMPLE VIII

Starting with an appropriately substituted benzyl mercaptan and methyl 1-chloromethyl-2-hydroxy-3-naphthoate and following, again, the procedure of Example I, the following congeners are prepared:



X	Y	X	Y
2-F	H	2-CH_3	H
2-Cl	H	3-CH_3	H
2-Br	H	4-CH_3	H
3-F	H	2-C_2H_5	H
3-Cl	H	4-C_2H_5	H
3-Br	H	2-i-C_3H_7	H
4-F	H	3-t-C_4H_9	H
4-Cl	H	4-t-C_4H_9	H
4-Br	H	4-n-C_4H_9	H
2CF_3	H	2-n-C_4H_9	H
3-CF_3	H	4-n-C_4H_9	H
4-CF_3	H	2-CH_3O	H
2-Cl	6-Cl	3-CH_3O	H
2-Cl	4-Cl	4-CH_3O	H
2-Cl	6-Br	2-C_2H_5O	H
2-Cl	4-Br	3-C_2H_5O	H
3-Cl	5-Cl	4-i-C_3H_7O	H
3-Cl	4-Cl	2-CH_3	4-CH_3O
4-Cl	2-F	3-CH_3	4-CH_3O
2-F	4-F	2-OCH_3	4-C_2H_5
2-F	6-F	2-CH_3	4-CH_3
2-Br	6-Br	2-CH_3	6-CH_3
2-Br	4-Br	2-i-C_3H_7	4-CH_3
2-Cl	4-CF_3	2-CH_3O	4-C_2H_5O
3-CF_3	5-Cl	2-CH_3	4-t-C_4H_9
3-CF_3	5-CF_3	2-HO	H
2-Br	4-CF_3	3-HO	H
2-NO_2	H	4-HO	H
3-NO_2	H	2-CH_3	4-HO
4-NO_2	H	3-CH_3O	4-HO
2-Cl	4-NO_2	2-C_2H_5O	4-HO
2-Br	4-NO_2	2-HO	4-i-C_3H_7O
3-Cl	5-NO_2	2-HO	4-C_2H_5
3-CF_3	5-NO_2	2-Br	4-C_2H_5
2-CH_3	4-NO_2	2-Br	3-CH_3
3-CH_3	4-NO_2	2-Br	6-CH_3O
2-NO_2	4-NO_2	2-Cl	6-CH_3O
2-CH_3O	4-NO_2	2-Cl	5-n-C_3H_7
2-NO_2	4-CH_3O	2-Cl	4-i-C_3H_7
3-NO_2	5-n-C_3H_7O	2-Cl	4-HO
2-C_2H_5	4-NO_2	3-Cl	2-HO
2-n-C_4H_9	5-NO_2	3-Cl	2-C_2H_5
3-HO	4-NO_2	3-Cl	2-t-C_4H_9
2-NO_2	4-HO	3-Cl	3-C_2H_5O
2-F	4-HO	4-Cl	2-CH_3
2-F	3-HO	4-Cl	2-i-C_3H_7
2-F	4-CH_3O	4-Cl	2-C_2H_5O
2-F	4-n-C_4H_9	4-Cl	2-HO
3-F	4-CH_3O	4-Cl	3-HO
3-F	4-NO_2	4-Cl	2-NO_2
3-F	4-C_2H_5	4-Cl	2-s-C_4H_9
4-F	2-CH_3	2-Cl	4-s-C_4H_9
4-F	2-C_2H_5	2-Br	4-s-C_4H_9
4-F	2-CH_3O	4-F	3-HO
4-F	3C_2H_5O	4-F	2-NO_2
4-F	3-n-C_3H_7	4-F	2-s-C_4H_9

along with their ethyl esters.

EXAMPLE IX

1-(o-Tolylthio)-2-hydroxy-3-naphthoic acid

To a solution of 11.1 g. of o-toluenesulfenyl chloride in 300 ml. of carbon tetrachloride is gradually added 14.1 g. of methyl 3-hydroxy-2-naphthoate and the resulting reaction mixture stirred at room temperature for 48 hours. The solvent is removed in vacuo and the residue, methyl 1-(o-tolylthio)-2-hydroxy-3-naphthoate, recrystallized from ethanol-chloroform, 9.0 g., m.p. 159°–160° C.

Four grams of the above ester in 50 ml. of ethanol containing 3 g. of potassium carbonate is heated to reflux for 18 hours, followed by filtration and evaporation to dryness. The residue is dissolved in water and acidified with 2N hydrochloric acid. The resulting precipitate is filtered and recrystallized from benzene to provide the pure product, 2.2 g., m.p. 200° C.

EXAMPLE X

Employing the procedure of Example IX and starting with the appropriate sulfenyl chloride, the following compounds are prepared:

1-Phenylthio-2-hydroxy-3-naphthoic acid, m.p. 225°–227° C.;

1-(m-Tolylthio)-2-hydroxy-3-naphthoic acid, m.p. 183°–186° C.;

1-(p-Chlorophenylthio)-2-hydroxy-3-naphthoic acid, m.p. 228°–230° C.; Cl

1-(o-Isopropylphenylthio)-2-hydroxy-3-naphthoic acid, m.p. 198°–200° C.;

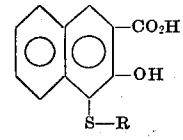
1-(m-Trifluoromethylphenylthio)-2-hydroxy-3-naphthoic acid, m.p. 228°–230° C.;

1-(2,4,6-Trimethylphenylthio)-2-hydroxy-3-naphthoic acid, m.p. 260° C.;

1-(2-Thiazolylthio)-2-hydroxy-3-naphthoic acid, m.p. 274° C.

EXAMPLE XI

The procedure of Example IX is repeated, starting with the requisite alkyl or cycloalkyl sulfenyl chloride, to provide the following analogs:



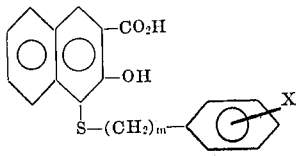
R	R
n-propyl	cyclopropyl
i-propyl	cyclobutyl
n-butyl	cyclopentyl
t-butyl	cyclohexyl
s-butyl	cycloheptyl
n-pentyl	4-methylcyclohexyl
2-methyl-n-butyl	cyclooctyl
3-methyl-n-butyl	4,4-dimethylcyclohexyl
n-hexyl	4-ethylcyclohexyl
2-methyl-n-pentyl	cyclononyl
4-methyl-n-pentyl	4,5-dimethylcycloheptyl
4,4-dimethyl-n-butyl	cyclooctyl
n-heptyl	cyclodecyl

4,4-dimethyl-n-pentyl
n-octyl
2,2,3,3-tetramethyl-n-pentyl
n-decyl
2,2,3-trimethyl-n-butyl
3,4,4-trimethyl-n-pentyl
n-nonyl

and their methyl esters.

EXAMPLE XII

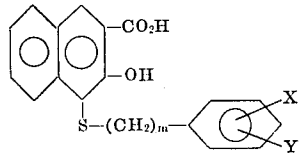
Starting with the required benzyl and monosubstituted benzyl and phenyl sulfenyl chlorides and repeating the procedures of Example IX, the following congeners are synthesized:



m	X	m	X
0	4-CH_3	0	4-F
0	4-t-C_4H_9	0	2-Br
0	2-C_2H_5	0	3-Br
0	4-C_2H_5	0	4-Br
0	2-n-C_3H_7	0	4-CF_3
0	4-i-C_4H_9	0	2-NO_2
0	2-CH_3O	0	3-NO_2
0	3-CH_3O	0	4-NO_2
0	4-CH_3O	1	H
0	2-C_2H_5O	1	2-F
0	4-n-C_4H_9O	1	3-F
0	4-i-C_3H_7O	1	4-F
0	2-HO	1	2-Cl
0	3-HO	1	3-Cl
0	4-HO	1	4-Cl
0	4-i-C_4H_9O	1	2-Br
0	2-Cl	1	3-Br
0	3-Cl	1	4-Br
0	4-Cl	1	2-CF_3
0	2-F	1	3-CF_3
0	3-F	1	4-CF_3
1	2-NO_2	1	3-C_2H_5O
1	3-NO_2	1	4-i-C_3H_7O
1	4-NO_2	1	2-HO
1	2-CH_3	1	3-HO
1	3-CH_3	1	4-HO
1	4-CH_3	1	2-C_2H_5
1	4-C_2H_5	1	2-i-C_3H_7
1	3-t-C_4H_9	1	4-t-C_4H_9
1	4-n-C_4H_9	1	2-n-C_4H_9
1	4-s-C_4H_9	1	2-CH_3O
1	3-CH_3O	1	4-CH_3O
1	2-C_2H_5O		

EXAMPLE XIII

The procedure of Example IX is again repeated, employing the appropriate disubstituted phenyl and benzyl sulfenyl chlorides, to provide the following products:



m	X	Y	m	X	Y
0	2-Cl	4-Cl	0	3-Cl	5-n-C_3H_7
0	2-Cl	6-Cl	0	2-F	4-CH_3
0	3-Cl	4-Cl	0	4-F	2-i-C_3H_7
0	3-Cl	5-Cl	0	4-Cl	2-i-C_3H_7
0	2-Br	3-Br	0	2-Br	4-C_2H_5O
0	2-Cl	4-Br	0	2-Br	4-n-C_3H_7O
0	2-Br	4-Br	0	2 -Br	3-CH_3O
0	2-Br	6-Br	0	2-Br	4-HO
0	3-Cl	5-Br	0	2-HO	4-Cl
0	2-F	4-F	0	2-CH_3	6-CH_3
0	2-F	4-Cl	0	2-C_2H_5	6-C_2H_5
0	3-F	5-F	0	2-CH_3	4-CH_3
0	2-F	6-F	0	3-CH_3	5-CH_3
0	2-Cl	5-CF_3	0	2-CH_3	4-C_2H_5
0	2-Br	5-CF_3	0	2-CH_3 4-t-C_4H_9	
0	2-F	2-CF_3	0	2-i-C_3H_7	4-CH_3
0	3-Cl	5-CF_3	0	3-n-C_3H_7	5-n-C_3H_7
0	2-F	3-F	0	2-CH_3	4-CH_3O
0	2-Br	4-t-C_4H_9	0	2-CH_3	3-C_2H_5O
0	2-CH_3O	6-CH_3O	0	3-NO_2	5-CF_3
0	2-CH_3O	4-CH_3	0	3-NO_2	6-CH_3O
0	2-CH_3O	4-HO	0	3-NO_2	4-n-C_4H_9O
0	3-HO	4-HO	0	4-NO_2	2-HO
0	2-CH_3	4-HO	0	4-NO_2	2-i-C_3H_7O
0	2-HO	4-CH_3	0	4-NO_2	2-C_2H_5O
0	2-C_2H_5O	4-HO	0	4-NO_2	2-F
0	3-HO	4-n-C_3H_7	0	3-NO_2	5-s-C_4H_9
0	2-CH_3	4-n-C_4H_9O	0	3-NO_2	5-HO
0	2-CH_3	4-t-C_4H_9	0	3-NO_2	4-F
0	2-CH_3	4-Cl	0	2-NO_2	6-CH_3
0	2-CH_3	4-Br	0	2-NO_2	6-Br
0	2-CH_3	4-F	0	2-NO_2	4-F
0	2-Cl	4-C_2H_5	0	2-NO_2	4-t-C_4H_9
0	2-NO_2	4-CH_3	1	2-Cl	6-Cl
0	2-NO_2	3-C_2H_5	1	2-Cl	4-Cl
0	2-NO_2	4-Cl	1	2-Cl	6-Br
0	3-NO_2	2-C_2H_5	1	2-Cl	4-Br
0	3-NO_2	6-CH_3	1	3-Cl	5-Cl
0	3-NO_2	6-i-C_3H_7	1	3-Cl	4-Cl
0	3-NO_2	5-n-C_4H_9	1	4-Cl	2-F
0	3-NO_2	4-Br	1	2-F	4-F
0	3-NO_2	4-Cl	1	2-F	6-F
0	4-NO_2	2-Cl	1	2-Br	6-Br
0	4-NO_2	3-Cl	1	2-Br	4-Br
0	4-NO_2	2-i-C_3H_7	1	2-Cl	4-CF_3
0	4-NO_2	2-Br	1	3-CF_3	5-Cl
0	4-NO_2	2-n-C_4H_9	1	3-CF_3	5-CF_3
0	2-NO_2	4-CH_3 O	1	2-Br	4-CF_3
0	2-NO_2	4-HO	1	2-CH_3	4-CH_3O
1	3-CH_3	4-CH_3O	1	4-F	2-CH_3
1	2-CH_3O	4-C_2H_5	1	4-F	2-C_2H_5
1	2-CH_3	4-CH_3	1	4-F	2-CH_3O
1	2-CH_3	6-CH_3	1	4-F	3-C_2H_5O
1	2-i-C_3H_7	4-CH_3	1	4-F	3-n-C_3H_7
1	2-CH_3O	4-C_2H_5O	1	4-F	3-HO
1	2-CH_3	4-t-C_4H_9	1	4-F	2-NO_2
1	2-CH_3	4-HO	1	4-F	2-s-C_4H_9
1	2-Cl	4-NO_2	1	3-CH_3O	4-HO
1	2-Br	4-NO_2	1	2-C_2H_5O	4-HO
1	3-Cl	5-NO_2	1	2-HO	4-i-C_3H_7O
1	3-CF_3	5-NO_2	1	2-HO	4-C_2H_5
1	2 -CH_3	4-NO_2	1	2-Br	4-C_2H_5
1	3-CH_3	4-NO_2	1	2-Br	3-CH_3
1	2-NO_2	4-NO_2	1	2-Br	6-CH_3O
1	3-CH_3O	4-NO_2	1	2-Cl	6-CH_3O
1	2-NO_2	4-CH_3O	1	2-Cl	5-n-C_3H_7
1	3-NO_2	5-n-C_3H_7O	1	2-Cl	4-i-C_3H_7
1	2-C_2H_5	4-NO_2	1	2-Cl	4-HO
1	2-n-C_4H_9	5-NO_2	1	3-Cl	2-HO
1	3-HO	4-NO_2	1	3-Cl	2-C_2H_5
1	2-NO_2	4-HO	1	3-Cl	2-t-C_4H_9
1	2-F	4-HO	1	3-Cl	3-C_2H_5O
1	2-F	3-HO	1	4-Cl	2-CH_3
1	2-F	4-CH_3O	1	4-Cl	2-i-C_3H_7
1	2-F	4-n-C_4H_9	1	4-Cl	2-C_2H_5O
1	3-F	4-CH_3O	1	4-Cl	2-HO
1	3-F	4-NO_2	1	4-Cl	3-HO
1	3-F	4-C_2H_5	1	4-Cl	2-NO_2
1	2-Br	4-s-C_4H_9	1	4-Cl	2-s-C_4H_9
			1	2-Cl	4-s-C_4H_9

and their ethyl esters.

EXAMPLE XIV

Using the appropriate aryl sulfenyl chloride and employing the experimental conditions of Example IX, the following naphthoic acids are prepared:

1-(2-Pyridylthio)-2hydroxy-3-naphthoic acid;
1-(3-Pyridylthio)-2-hydroxy-3-naphthoic acid;
1-(4-Pyridylthio)-2-hydroxy-3-naphthoic acid;
1-(1-Naphthylthio)-2-hydroxy-3-naphthoic acid;
1-(2-Naphthylthio)-2-hydroxy-3-naphthoic acid.

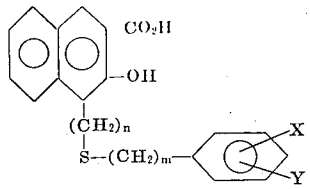
EXAMPLE XV

1-(p-Aminophenylthiomethyl)-2-hydroxy-3-naphthoic acid

A suspension of 3.55 g. of 1-(p-nitrophenylthiomethyl)-2-hydroxy-3-naphthoic acid in 48 ml. of 12N hydrochloric acid is treated with 1.0 g. of stannous chloride and the mixture heated for 3 hours at 60° C. and then allowed to stir at room temperature until a complete solution is effected. The resulting solution is made basic with ammonium hydroxide and the tin hydroxide filtered. The filtrate is gradually made acidic with glacial acetic acid until a precipitate no longer forms. The desired product is filtered, dried and further purified by recrystallization from methanol-water.

EXAMPLE XVI

The reduction procedure of Example XV is followed, using the corresponding nitro substituted phenylthio-, phenylthiomethyl-, benzylthio- and benzylthiomethyl-substituted naphthoic acid, to provide the following compounds:



n	m	X	Y
1	0	2-NH_2	H
1	0	3-NH_2	H
1	0	4-NH_2	H
1	0	2-NH_2	4-CH_3
1	0	2-NH_2	3-C_2H_5
1	0	2-NH_2	4-Cl
1	0	3-NH_2	2-C_2H_5
1	0	3-NH_2	3-CH_3
1	0	3-NH_2	6-i-C_3H_7
1	0	3-NH_2	5-n-C_4H_9
1	0	3-NH_2	4-Br
1	0	3-NH_2	4-Cl
1	0	4-NH_2	2-Cl
1	0	4NH_2	3-Cl
1	0	4-NH_2	2-i-C_3H_7
1	0	4-NH_2	2-Br
1	0	4-NH_2	2-n-C_4H_9
1	1	2-NH_2	H
1	1	3-NH_2	H
1	1	4-NH_2	H
1	1	2-Cl	4-NH_2
1	1	2-Br	4-NH_2
1	1	3-Cl	5-NH_2
1	1	3-CF_3	5-NH_2
1	1	2-CH_3	4-NH_2
1	1	3-CH_3	4-NH_2
1	1	2-NH_2	4-NH_2
1	1	2-CH_3O	4-NH_2
1	1	2-NH_2	4-CH_3O
1	1	3-NH_2	5-n-C_3H_7O
1	1	2-C_2H_5	4-NH_2
1	1	2-n-C_4H_9	5-NH_2
1	1	3-HO	4-NH_2
1	1	2-NH_2	4-HO
1	1	3-F	4-NH_2
1	1	4-F	2-NH_2
1	1	4-Cl	2-NH_2
0	0	2-NH_2	H
0	0	3-NH_2	H
0	0	4-NH_2	H
0	1	2-NH_2	H
0	1	3-NH_2	H
0	1	4-NH_2	H
0	0	2-NH_2	3-C_2H_5
0	0	3-NH_2	2-C_2H_5
0	1	2-Br	4-NH_2
0	1	3-CF_3	5-NH_2
0	1	3-CH_3	4-NH_2
0	1	2-NH_2	4-CH_3O
0	1	2-C_2H_5	4-NH_2
0	1	3-F	4-NH_2
0	1	4-Cl	2-NH_2
1	0	2-NH_2	4-CH_3O
1	0	2-NH_2	4-HO
1	0	3-NH_2	5-CF_3
1	0	3-NH_2	6-CH_3O
1	0	3-NH_2	4-n-C_4H_9O
1	0	4-NH_2	2-HO
1	0	4-NH_2	2-i-C_3H_7O
1	0	4-NH_2	2-C_2H_5O
1	0	4-NH_2	5-s-C_4H_9
1	0	3-NH_2	5-HO
1	0	3-NH_2	4-F
1	0	2-NH_2	6-CH_3
1	0	2-NH_2	6-Br
1	0	2-NH_2	4-F
1	0	2-NH_2	4-t-C_4H_9
0	0	3-NH_2	6-CH_3
0	0	3-NH_2	6-i-C_3H_7
0	0	3-NH_2	5-n-C_4H_9
0	0	3-NH_2	4-Br
0	0	3-NH_2	4-Cl
0	0	4-NH_2	2-Cl
0	0	4-NH_2	2-Br
0	0	4-NH_2	3-Cl
0	0	4-NH_2	2-CH_3
0	0	4-NH_2	3-OCH_3
0	0	4-NH_2	3-NH_2
0	0	4-NH_2	2-n-C_4H_9
0	0	4-NH_2	4-F
0	0	4-NH_2	2-HO
0	0	4-NH_2	4-HO
0	0	4-NH_2	5-CF_3
0	0	4-NH_2	6-CH_3O
0	0	4-NH_2	4-n-C_4H_9O
0	0	4-NH_2	2-HO
0	0	4-NH_2	2-i-C_3H_7O
0	0	4-NH_2	2-C_2H_5O
0	0	4-NH_2	5-s-C_4H_9
0	0	4-NH_2	5-HO
0	0	4-NH_2	4-F
0	0	4-NH_2	6-CH_3
0	0	4-NH_2	6-Br
0	0	4-NH_2	4-F
0	0	4-NH_2	4-t-C_4H_9
0	0	4-NH_2	4-CH_3
0	0	4-NH_2	4-Cl
0	0	4-NH_2	2-NH_2
0	0	4-NH_2	5-NH_2
0	0	4-NH_2	4-NH_2
0	0	4-NH_2	5-i-C_3H_7O
0	0	4-NH_2	5-NO_2
0	0	4-NH_2	2-NH_2

EXAMPLE XVII

1-(p-Acetamidophenylthiomethyl)-2-hydroxy-3-naphthoic acid

A. Anhydride Method

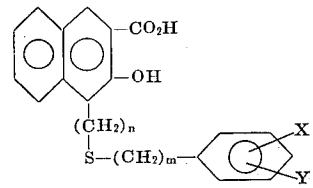
To a solution of 3.25 g. of 1-(p-aminophenylthiomethyl)-2-hydroxy-3-naphthoic acid in 35 ml. of chloroform is added dropwise 1.12 g. of acetic anhydride and the resulting solution heated to reflux for 2 hours. The excess reagent and solvent is removed under reduced pressure and the residual product recrystallized from ethanol. The product proves to be identical to that prepared in Example II.

B. Acid Chloride Method

To a solution of 4.87 g. of 1-(p-aminophenylthiomethyl)-2-hydroxy-3-naphthoic acid in 40 ml. of pyridine and cooled to 10° C. is added slowly 1.33 g. of acetyl chloride and the resulting solution heated in a water bath to 75° C. for 4 hours. The excess reagent and solvent is removed in vacuo, the residue dissolved in a minimum amount of water and sufficient 3N hydrochloride acid added to precipitate the product. The solid which is filtered, dried and recrystallized from isopropanol is identical to that prepared by the Anhydride Method above and Example II.

EXAMPLE XVIII

Starting with the suitable amino compound and requisite acylating reagent, and following the appropriate procedure method in Example XVII, the following congeners are synthesized:



Method	X	Y	n	m
Anhydride	2-$NHCOCH_3$	H	1	0
Anhydride	2-$NHCOCH_2CH_3$	H	1	0
Anhydride	3-$NHCOCH_3$	H	1	0
Anhydride	3-NHCHO	H	1	0
Anhydride	3-$NHCOCH(CH_3)_2$	H	1	0
Acid Chloride	3-$NHSO_2C_6H_5$	H	1	0
Anhydride	4-$NHCO(CH_2)_2CH_3$	H	1	0
Anhydride	4-NHCHO	H	1	0
Anhydride	4-$NHCOCH(CH_3)_2$	H	1	0
Acid Chloride	4-$NHSO_2C_6H_5$	H	1	0
Anhydride	2-$NHCOCH_3$	4-CH_3	1	0
Anhydride	2-$NHCOCH_3$	4-Cl	1	0
Acid Chloride	2-$NHCO(CH_2)_2CH_3$	4-Cl	1	0
Anhydride	3-$NHCOCH_3$	2-C_2H_5	1	0
Anhydride	3NHCHO	2-C_2H_5	1	0
Anhydride	3-$NHCOCH_3$	6-CH_3	1	0
Acid Chloride	3-$NHSO_2C_6H_5$	6-CH_3	1	0
Acid Chloride	3-$NHCO(CH_2)_2CH_3$	6-CH_3	1	0
Acid Chloride	4-$NHCOCH(CH_3)_2$	2-Cl	1	0
Acid Chloride	4-$NHCOCH(CH_3)_2$	2-Br	1	0
Anhydride	2-$NHCOCH_3$	4-CH_3O	1	0
Anhydride	3-$NHCOCH_3$	4-n-C_4H_9O	1	0
Anhydride	4-$NHCOCH_3$	2-i-C_3H_7O	1	0
Anhydride	2-NHCHO	6-Br	1	0
Anhydride	2-NHCHO	4-t-C_4H_9	1	0
Anhydride	2-$NHCOCH_3$	H	1	1
Anhydride	4-$NHCOCH_3$	H	1	1
Anhydride	4-$NHCOCH_3$	2-Cl	1	1
Anhydride	4-$NHCOCH_3$	2-Br	1	1
Acid Chloride	4-$NHCOCH(CH_3)_2$	2-Br	1	1
Anhydride	5-$NHCOCH_3$	3-CF_3	1	1
Anhydride	4-$NHCOCH_2CH_3$	2-C_2H_5	1	1
Anhydride	2-$NHCOCH_3$	4-OH	1	1
Anhydride	3-$NHCOCH_3$	H	0	0
Acid Chloride	3-$NHSO_2C_6H_5$	H	0	0
Acid Chloride	4-$NHSO_2C_6H_5$	H	0	0

Anhydride	2-NHCOCH$_3$	H	0	1	0	0	2-NHCH$_3$ 4-CH$_3$	0	1	3-N(CH$_3$)$_2$	5-n-C$_3$H$_7$O
Anhydride	4-NHCOCH(CH$_3$)$_2$	H	0	1	0	0	2-N(CH$_3$)$_2$ 4-Cl	0	1	2-NH-n-C$_3$H$_7$	4-F
Anhydride	4-NHCO(CH$_2$)$_2$CH$_3$	H	0	1	0	0	3-N(CH$_3$)$_2$ 2-C$_2$H$_5$	0	1	5-NHCH$_3$	3-CH$_3$
Anhydride	2-NHCOCH$_3$	3-C$_2$H$_5$	0	0	0	0	3-NHCH$_3$ 6-CH$_3$				
Anhydride	2-NHCOCH$_3$	4-Cl	0	0	0	0	3-NHC$_2$H$_5$ 4-Br				
Anhydride	3-NHCHO	6-CH$_3$	0	0	0	0	4-N(CH$_3$)$_2$ 2-i-C$_3$H$_7$				
Acid Chloride	3-NHSO$_2$C$_6$H$_5$	6-CH$_3$	0	0	0	0	4-N(C$_2$H$_5$)$_2$ 2-i-C$_3$H$_7$				
Anhydride	4-NHCO(CH$_2$)$_2$CH$_3$	2-Br	0	0	0	0	2-N(CH$_3$)$_2$ 4 -CH$_3$0				
Anhydride	4-NHCO(CH$_2$)$_2$CH$_3$	2-i-C$_3$H$_7$	0	0	0	0	2-N(CH$_3$)$_2$ 4-HO				
Anhydride	4-NHCOCH$_3$	2-i-C$_3$H$_7$O	0	0	0	0	4-N(C$_2$H$_5$)$_2$ 2-C$_2$H$_5$0				
Anhydride	4-NHCOCH$_3$	2-F	0	0							
Anhydride	3-NHCOCH$_3$	5-s-C$_4$H$_9$	0	0							
Anhydride	4-NHCOCH$_3$	2-Cl	0	1							
Anhydride	4-NHCOCH$_2$CH$_3$	2-Cl	0	1							
Anhydride	4-NHCOCH(CH$_3$)$_2$	2-Br	0	1							
Anhydride	5-NHCHO	3-Cl	0	1							
Anhydride	5-NHCOCH$_3$	3-Cl	0	1							
Anhydride	4-NHCOCH$_3$	2-CH$_3$	0	1							
Acid Chloride	4-H NHSO$_2$C$_6$H$_5$	2-CH$_3$	0	1							
Acid Chloride	4-NHSO$_2$C$_6$H$_5$	3-CH$_3$	0	1							
Acid Chloride	4-NHCO(CH$_2$)$_2$ CH$_3$	3-CH$_3$O	0	1							
Anhydride	2-NHCOCH$_3$	4-CH$_3$O	0	1							
Anhydride	3-NHCHO	5-n-C$_3$H$_7$O	0	1							
Anhydride	4-NHCOCH$_3$	2-C$_2$H$_5$	0	1							
Anhydride	4-NHCOCH$_3$	3-F	0	1							
Anhydride	2-NHCOCH$_3$	4-Cl	0	1							

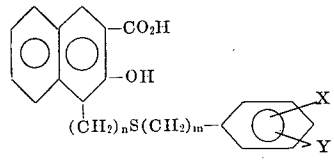
EXAMPLE XIX

1-(p-Dimethylaminophenylthiomethyl)-2-hydroxy-3-naphthoic acid

To a solution of 6.5 g. of 1-(p-aminophenylthiomethyl)-2-hydroxy-3-naphthoic acid in 75 ml. of water containing 6.4 g. of sodium carbonate is added slowly, with rapid stirring, 6.2 g. of methyl iodide. The reaction is heated to reflux for 6 hours and is then cooled and made acid to Congo red paper by the gradual addition of 6N hydrochloric acid. The resulting precipitate is filtered, dried and recrystallized from ethanol-water.

EXAMPLE XX

Employing the general alkylation procedure of Example XIX and starting with the requisite amount of alkyl iodide and appropriate amino compound the following congeners are synthesized in moderate yields:



n	m	X	Y
1	0	3-N(CH$_3$)$_2$	H
1	0	3-NHC$_2$H$_5$	H
1	0	3-N(n-C$_3$H$_7$)$_2$	H
1	0	4-N(C$_2$H$_5$)$_2$	H
1	0	4-NH-i-C$_3$H$_7$	H
1	0	4-N(n-C$_4$H$_9$)$_2$	H
1	0	2-NHCH$_3$	4-Cl
1	0	3-N(CH$_3$)$_2$	6-i-C$_3$H$_7$
1	0	3-N(CH$_3$)$_2$	6-CH$_3$
1	0	3-N(CH$_3$)$_2$	4-Cl
1	0	4-N(CH$_3$)$_2$	3-Cl
1	0	4-N(C$_2$H$_5$)$_2$	2-Br
1	0	4-NH-n-C$_4$H$_9$	2-Br
1	0	2 -NH-n-C$_3$H$_7$	4-CH$_3$0
1	0	3-N(CH$_3$)$_2$	5-CF$_3$
1	0	4-N(CH$_3$)$_2$	2-F
0	1	2-N(CH$_3$)$_2$	H
0	1	2-NHC$_2$H$_5$	H
0	1	3-N(C$_2$H$_5$)$_2$	H
0	1	3-N-i-C$_4$H$_9$	H
0	1	3-N(n-C$_4$H$_9$)$_2$	H
0	1	4-N(CH$_3$)$_2$	H
0	1	4-N(C$_2$H$_5$)$_2$	H
0	1	4-N(i-C$_3$H$_7$)$_2$	H
0	1	4-NH-n-C$_4$H$_9$	H

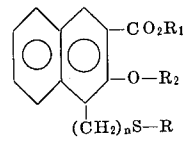
n	m	X	Y
1	1	2-NCHCH$_3$	H
1	1	2-N(CH$_3$)$_2$	H
1	1	4-N(C$_2$H$_5$)$_2$	H
1	1	4-N(n-C$_3$H$_7$)$_2$	H
1	1	4-N(CH$_3$)$_2$	2-Cl
1	1	4-N(CH$_3$)$_2$	3-Cl
1	1	4-N(C$_2$H$_5$)$_2$	2-CH$_3$
1	1	4-N(n-C$_4$H$_9$)$_2$	2-CH$_3$O
1	1	4-NH-s-C$_4$H$_9$	2-CH$_3$
1	1	5-N(CH$_3$)$_2$	2-n-C$_4$H$_9$
1	1	4-N(CH$_3$)$_2$	3-F
1	1	2-N(C$_2$H$_5$)$_2$	4-F
0	0	2-N(CH$_3$)$_2$	H
0	0	3-N(C$_2$H$_5$)$_2$	H
0	0	3-NH-n-C$_3$H$_7$	H
0	0	3-NH-s-C$_4$H$_9$	H
0	0	4-N(CH$_3$)$_2$	H
0	0	3-N(CH$_3$)$_2$	4-F
0	1	4-NH-n-C$_3$H$_7$	2-Cl
0	1	4-N(CH$_3$)$_2$	2-Br
0	1	4-N(C$_2$H$_5$)$_2$	2-Br
0	1	4-NH-s-C$_4$H$_9$	2-Br
0	1	4-N(CH$_3$)$_2$	2-CH$_3$
0	1	4-N(C$_2$H$_5$)$_2$	3-CH$_3$0
0	1	4-N(C$_2$H$_5$)$_2$	2-C$_2$H$_5$

EXAMPLE XXI

1-(o-Isopropylphenylthiomethyl)-2-acetoxy-3-naphthoic acid

To a solution of 40 ml. of chloroform containing 3.52 g. of 1-(o-isopropylphenylthiomethyl)-2-hydroxy-3-naphthoic acid is added 1.02 g. of acetic anhydride and the resulting solution heated to reflux for 3 hours on a steam bath. The solvent is removed under reduced pressure and the residual acetoxy compound recrystallized from methanol-water.

By a similar procedure, and employing the requisite anhydride and naphthoic acid or ester, the following congeners are synthesized:



R	R$_1$	R$_2$	n
o-CH$_3$C$_6$H$_4$	H	COCH$_3$	1
o-CH$_3$C$_6$H$_4$	CH$_3$	COCH$_3$	1
o-ClC$_6$H$_4$	H	CO(CH$_2$)$_2$CH$_3$	1
m-BrC$_6$H$_4$	H	CHO	1
p-BrC$_6$H$_4$	H	COCH$_3$	1
p-ClC$_6$H$_4$	H	COCH$_3$	0
p-ClC$_6$H$_4$	G	COCH$_3$	1
m-CH$_3$C$_6$H$_4$	CH$_3$	COCH(CH$_3$)$_2$	1
m-CH$_3$C$_6$H$_4$	C$_2$H$_5$	COCH$_3$	1
m-CH$_3$C$_6$H$_4$	H	COCH$_3$	1
p-CH$_3$C$_6$H$_4$	CH$_3$	COCH$_3$	1
2,3-Cl$_2$C$_6$H$_3$	H	COCH$_3$	1
2,3-Cl$_2$C$_6$H$_3$	CH$_3$	COCH$_3$	1
2,3-Cl$_2$C$_6$H$_3$	n-C$_3$H$_7$	COCH$_3$	1
n-C$_3$H$_7$	H	CHO	1
n-C$_6$H$_{13}$	n-C$_3$H$_7$	CO(CH$_2$)$_2$CH$_3$	1
n-C$_6$H$_{13}$	n-C$_3$H$_7$	CO(CH$_2$)$_2$CH$_3$	0
o-ClC$_6$H$_4$CH$_2$	H	COCH$_3$	0
o-ClC$_6$H$_4$CH$_2$	CH$_3$	COCH$_3$	0
o-ClC$_6$H$_4$CH$_2$	H	COCH$_2$CH$_3$	1
o-BrC$_6$H$_4$CH$_2$	H	COCH$_3$	0
2,6-Cl(Br)C$_6$H$_3$CH$_2$	H	COCH$_3$	0
2,4-Br(C$_2$H$_5$)C$_6$H$_3$CH$_2$	H	COCH(CH$_3$)$_2$	0
3,4-CH$_3$(NO$_2$)C$_6$H$_3$CH$_2$	H	COCH$_3$	0
4,2-F(NO$_2$)C$_6$H$_3$CH$_2$	H	COCH$_3$	0
4-(CH$_3$)$_2$NC$_6$H$_4$	H	COCH$_3$	0
4-(CH$_3$)$_2$NC$_6$H$_4$	H	COCH$_3$	1

EXAMPLE XXII

Potassium 1-phenylthiomethyl-2-hydroxy-3-naphthoate

To a solution of 3.1 g of 1-phenylthiomethyl-2-hydroxy-3-naphthoic acid dissolved in 30 ml. of methanol is added 561 mg. of potassium hydroxide and the resulting turbid solution concentrated to dryness in vacuo. The resulting potassium salt is triturated with acetone and filtered.

In a similar manner, starting with the appropriate alkali metal hydroxide, the corresponding lithium, sodium, rubidium and cesium salts are prepared.

EXAMPLE XXIII

Following the procedure of Example XXII, substituting water for methanol and employing the appropriate alkali earth metal hydroxide, the corresponding beryllium, calcium, magnesium, barium and strontium salts are prepared.

EXAMPLE XXIV

Ammonium 1-benzylthio-2-hydroxy-3-naphthoate

To a solution of 6.2 g. of 1-benzylthio-2-hydroxy-3-naphthoic acid in methanol is added sufficient ammonia to render the solution strongly alkaline. The excess ammonia and solvent are removed under reduced pressure and the residual ammonium salt triturated with isopropanol and filtered.

In a similar manner other organic amines are substituted for ammonia to provide the corresponding amine salts.

EXAMPLE XXV

Tablets

A tablet base is prepared by blending the following ingredients in the proportion by weight indicated:

Sucrose, U.S.P.	80.3
Tapioca starch	13.2
Magnesium stearate	6.5

Into this tablet base there is blended sufficient 1-(o-Isopropylphenylthiomethyl)-2-hydroxy-3-naphthoic acid to provide tablets containing 20, 100 and 250 mg. of active ingredient per tablet. The compositions are each compressed into tablets, each weighing 360 mg., by conventional means.

EXAMPLE XXVI

Capsules

A blend is prepared containing the following ingredients:

Calcium carbonate, U.S.P.	17.6
Dicalcium phosphate	18.8
Magnesium trisilicate, U.S.P.	5.2
Lactose, U.S.P.	5.2
Potato starch	5.2
Magnesium stearate A	0.8
Magnesium stearate B	0.35

To this blend is added sufficient sodium 1-(o-Isopropylphenylthiomethyl)-2-hydroxy-3-naphthoate to provide capsules containing 20, 100 and 250 mg. of active ingredient per capsule. The compositions are filled into conventional hard gelatin capsules in the amount of 350 mg. per capsule.

EXAMPLE XXVII

Injectable Preparation

One thousand grams of sodium 1-(o-bromophenylthiomethyl)-2-hydroxy-3-naphthoate are intimately mixed and ground with 2,500 grams of sodium ascorbate. The ground dry mixture is placed in vials and sterilized with ethylene oxide after which the vials are sterilely stoppered. For intravenous administration, sufficient water is added to the materials in the vials to form a solution containing 10 mg. of active ingredient per milliliter of injectable solution.

EXAMPLE XXVIII

Suspension

A suspension of 1-(o-bromophenylthiomethyl)-2-hydroxy-3-naphthoic acid is prepared with the following composition:

Effective ingredient	25.00 g.
70% aqueous sorbitol	741.29 g.
Glycerine, U.S.P.	185.35 g.
Gum acacia (10% solution)	100.00 ml.
Polyvinylpyrrolidone	0.50 g.
Distilled water	Sufficient to make 1 liter

To this suspension, various sweeteners and flavorants are added to improve the palatability of the suspension. The suspension contains approximately 25 mg. of effective agent per milliliter.

EXAMPLE XXIX

Solution

A solution of sodium 1-(1,1,3,3-tetramethyl-n-butylthiomethyl)-2-hydroxy-3-naphthoate is prepared with the following composition:

Effective ingredient	30.22 grams
Magnesium chloride hexahydrate	12.36 grams
Monoethanolamine	8.85 ml.
Propylene glycol	376.00 grams
Water, distilled	94.00 ml.

The resultant solution has a concentration of effective ingredient of 50 mg./ml. and is suitable for parenteral and especially for intramuscular administration.

PREPARATION A

Alkyl- and Cycloalkylmercaptans

The procedure of Urquhart, et al., Org. Syn., Col. Vol. 3, 363, which comprises alkylation of thiourea with an equimolar amount of an alkyl or cycloalkyl halide, formed by hydrolysis of the resulting isothiouronium salt, is employed in the preparation of the following mercaptans not previously reported in the chemical literature:

R-SH

R	R
2-methyl-n-pentyl	cyclopropyl
4-methyl-n-pentyl	cyclobutyl
4,4-dimethyl-n-butyl	4,4-dimethylcyclohexyl
4,4-dimethyl-n-pentyl	4-ethylcyclohexyl
2,2,3-trimethyl-n-butyl	cyclooctyl
3,4,4-trimethyl-n-pentyl	cyclononyl
2,2,3,3-tetramethyl-n-pentyl	4,5-dimethylcycloheptyl
	cyclodecyl

PREPARATION B

Benzenethiols

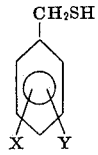
The following thiophenols not previously reported in the literature are synthesized by the method of Newman, et al., J. Org. Chem., 31, 3980 (1966), which employs acylation of a substituted phenol with dimethylthiocarbamyl chloride, thermal rearrangement to the s-aryl dimethylthiocarbamate and subsequent hydrolysis to the benzenethiol:

X	Y	X	Y
2-nitro	4-methyl	2-nitro	6-methyl
2-nitro	3-ethyl	2-nitro	6-bromo
3-nitro	2-ethyl	2-methyl	4-ethyl
3-nitro	6-methyl	2-methyl	4-t-butyl
3-nitro	6-i-propyl	2-i-propyl	4-methyl
3-nitro	5-n-butyl	3-n-propyl	5-n-propyl
2-nitro	4-hydroxy	2-methyl	4-methoxy
3-nitro	5-trifluoro-methyl	2-methyl	3-ethoxy
3-nitro	6-methoxy	2-methoxy	4-hydroxy
3-nitro	4-n-butoxy	2-hydroxy	H
4-nitro	2-hydroxy	3-hydroxy	H
4-nitro	2-i-propoxy	3-hydroxy	4-hydroxy
3-nitro	5-s-butyl	2-hydroxy	4-methyl
3-nitro	5-hydroxy	2-methyl	4-hydroxy
2-methyl	4-n-butoxy	2-ethoxy	4-hydroxy
2-methyl	4-t-butyl	3-hydroxy	4-n-propyl
2-methyl	4-chloro	2-methyl	4-bromo
2-methyl	4-fluoro	2-bromo	3-bromo
3-chloro	5-n-propyl	3-chloro	5-bromo
2-fluoro	4-methyl	3-fluoro	5-fluoro
4-fluoro	2-i-propyl	2-chloro	5-trifluoro-methyl
2-bromo	3-methoxy	2-bromo	5-trifluoro-methyl
2-bromo	4-hydroxy	2-fluoro	5-trifluoro-methyl
2-hydroxy	4-chloro	H	4-trifluoro-methyl
3-trifluoromethyl	4-methyl	3-chloro	5-trifluoro-methyl
3-trifluoromethyl	6-methyl		
3-trifluoromethyl	5-ethyl		
3-trifluoromethyl	2-methyl		

PREPARATION C

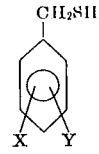
Benzylmercaptans

A. Employing the method of Kipnis, et al., J. Am. Chem. Soc., 71, 2270 (1949), which comprises reaction of an aromatic aldehyde with ethanolic ammonium hydrogen sulfide followed by reduction of the resulting disulfide with aluminum amalgam, is used to prepare the following α-toluenethiols not previously reported in the chemical literature:



X	Y	X	Y
3-bromo	H	4-ethyl	H
2-trifluoro-methyl	H	2-i-propyl	H
3-trifluoro-methyl	H	3-t-butyl	H
4-trifluoro-methyl	H	4-t-butyl	H
2-chloro	6-bromo	4-n-butyl	H
2-chloro	4-bromo	2-n-butyl	H
3-chloro	5-chloro	3-methoxy	H
4-chloro	2-fluoro	2-ethoxy	H
2-fluoro	4-fluoro	3-ethoxy	H
2-fluoro	6-fluoro	4-i-propoxy	H
2-bromo	6-bromo	2-methyl	4-methoxy
2-bromo	4-bromo	3-methyl	4-methoxy
2-chloro	4-trifluoromethyl	2-methoxy	4-ethyl
5-chloro	3-trifluoromethyl	2-methyl	4-methyl
3-trifluoro-methyl	5-trifluoromethyl	2-methyl	6-methyl
2-bromo	4-trifluoromethyl	2-i-propyl	4-methyl
2-ethyl	H	2-methoxy	4-ethoxy
2-methyl	4-t-butyl	2-ethoxy	4-hydroxy
2-hydroxy	H	2-hydroxy	4-i-propoxy
3-hydroxy	H	2-hydroxy	4-ethyl
4-hydroxy	H	2-bromo	4-ethyl
2-methyl	4-hydroxy	2-bromo	3-methyl
2-fluoro	4-hydroxy	2-bromo	6-methoxy
2-fluoro	3-hydroxy	2-chloro	6-methoxy
2-fluoro	4-methoxy	2 -chloro	5-n-propyl
2-fluoro	4-n-butyl	2-chloro	4-i-propyl
3-fluoro	4-methoxy	2-chloro	4-hydroxy
3-fluoro	4-ethyl	3-chloro	2-hydroxy
4-fluoro	2-methyl	3-chloro	2-ethyl
4-fluoro	2-ethyl	3-chloro	2-t-butyl
4-fluoro	2-methoxy	3-chloro	2-ethoxy
4-fluoro	3-ethoxy	4-chloro	2-methyl
4-fluoro	3-n-propyl	4-chloro	2-i-propyl
4-fluoro	3-hydroxy	4-chloro	2-ethoxy
4-fluoro	2-s-butyl	4-chloro	2-hydroxy
3-methoxy	4-hydroxy	4-chloro	3-hydroxy
2-bromo	4-s-butyl	4-chloro	2-s-butyl
		2-chloro	4-s-butyl

B. Previously unreported α-toluenethiols substituted with a nitro group in the aromatic moiety are prepared by the general method as outlined in Preparation A and comprises s-alkylation of thiourea with the corresponding benzyl halide followed by hydrolysis of the formed isothiouronium salt. Employing this method, the following compounds are synthesized:



X	Y	X	Y
2-chloro	4-nitro	2-ethyl	4-nitro
2-bromo	4-nitro	2-n-butyl	5-nitro
3-chloro	5-nitro	3-hydroxy	4-nitro
3-trifluoromethyl	5-nitro	2-nitro	4-hydroxy
2-methyl	4-nitro	3-fluoro	4-nitro
3-methyl	4-nitro	4-fluoro	2-nitro
2-nitro	4-nitro		
2-methoxy	4-nitro		
3-nitro	5-n-proxy		

PREPARATION D

Alkyl- and Cycloalkylsulfenyl chlorides

Using the method of Himel, U.S. Pat. No. 2,934,563, which employs s-chlorination of mercaptans, the following sulfenyl chlorides not reported in the literature are prepared:

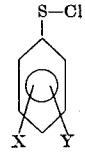
R-S-Cl

R	R
n-butyl	n-octyl
s-butyl	3,4,4-trimethyl-n-pentyl
n-pentyl	2,2,3,3-tetramethyl-n-pentyl
2-methyl-n-butyl	n-nonyl
3-methyl-n-butyl	n-decyl
n-hexyl	cyclopropyl
2-methyl-n-pentyl	cyclobutyl
4-methyl-n-pentyl	4-methylcyclohexyl
4,4-dimethyl-n-pentyl	4,4-dimethylcyclohexyl
4,4-dimethyl-n-butyl	4-ethyl
2,2,3-trimethyl-n-butyl	cyclononyl
4,5-dimethylcycloheptyl	cyclodecyl

PREPARATION E

Benzenesulfenyl Chlorides

The following benzenesulfenyl chlorides not previously reported in the chemical literature, are prepared according to the method of Almasi, et al., Chem. Ber., 94, 725 (1961), which comprises s-chlorination of the appropriately substituted thiophenol in dry carbon-tetrachloride using chlorine gas:



X	Y	X	Y

2-C_2H_5	H	3-Cl
4-C_2H_5	H	2-Br
2-n-C_3H_7	H	2-Cl
4-i-butyl	H	2-Cl
3-CH_3O	H	2-Br
2-C_2H_5O	H	2-Br
4-n-C_4H_9O	H	2-Br
4-i-C_3H_7O	H	3-Cl
2-HO	H	2-F
3-HO	H	2-F
4-HO	H	3-F
4-i-C_4H_9O	H	2-F
2-F	H	2-Cl
3-F	H	2-Br
3-Br	H	2-F
4-CF_3	H	3-Cl
2-Cl	6-Cl	2-F
2-Br	4-t-C_4H_9	2Cl
3-Cl	5-n-C_3H_7	2-NO_2
2-F	4-CH_3	3-NO_2
4-F	2-i-C_3H_7	3-NO_2
4-Cl	2-i-C_3H_7	3-NO_2
2-Br	4-C_2H_5O	3NO_2
2-Br	4-n-C_3H_7O	3-NO_2
2-Br	3-CH_3O	3-NO_2
2-Br	4-HO	4-NO_2
2-HO	4-Cl	4-NO_2
2-CH_3	6-CH_3	4-NO_2
2-C_2H_5	6-C_2H_5	4-NO_2
2-CH_3	4-C_2H_5	4-NO_2
2-CH_3	4-t-C_4H_9	3-NO_2
2 -i-C_3H_7	4-CH_3	3-NO_2
3-n-C_3H_7	5-n-C_3H_7	3-NO_2
2CH_3	4-CH_3O	4-NO_2
2-CH_3	3-C_2H_5O	4-NO_2
2-CH_3O	6-CH_3O	4-NO_2
2-CH_3O	4-CH_3	4-NO_2
2-CH_3O	4-HO	3-NO_2
3-HO	4-HO	3-NO_2
2-CH_3	4-HO	3-NO_2
2-HO	4-CH_3	3-NO_2
2-C_2H_5O	4-HO	3-NO_2
3-HO	4-n-C_3H_7	3-NO_2
3-CH_3	4-n-C_4H_9O	3-NO_2
2-CH_3	4-t-C_4H_9	
2-CH_3	4-Cl	
2-CH_3	4-F	

5-Cl	3-CF_3	5-CF_3
3-Br	2-Br	4-CF_3
4-Br	2-CH_3	4-CH_3O
4-Br	3-CH_3	4-CH_3O
4-Br	2-CH_3O	4-C_2H_5
4-Br	2-CH_3	4-CH_3
6-Br	2-CH_3	6-CH_3
5-Br	2-i-C_3H_7	4-CH_3
4-F	2-CH_3O	4-C_2H_5O
4-Cl	2-CH_3	4-t-C_4H_9
5-F	2-CH_3	4-HO
6-F	2-Cl	4-NO_2
5-CF_3	2-Br	4-NO_2
5-CF_3	3-Cl	5-NO_2
5-CF_3	3-CF_3	5-NO_2
5-CF_3	2-CH_3	4-NO_2
3-F	3-CH_3	4-NO_2
4-C_2H_5	2-NO_2	4-NO_2
3-C_2H_5	3-CH_3O	4-NO_2
2C_2H_5	2-NO_2	4-CH_3O
6-CH_3	3-NO_2	5-n-C_3H_7O
6-i-C_3H_7	2-C_2H_5	4-NO_2
5-n-C_4H_9	2-n-C_4H_9	5-NO_2
4-Br	3-HO	4-NO_2
4-Cl	2-NO_2	4-HO
2-Cl	4-Cl	2-CH_3
3-Cl		
2-i-C_3H_7		
2-Br		
2-n-C_4H_9		
5-CF_3		
3-CH_3O		
4-n-C_4H_9O		
2-HO		
2-i-C_3H_7O		
2-C_2H_5O		
2-F		
5-s-C_4H_9		
5-HO		
4-F		
6-CH_3		
6-Br		
4-F		
4-t-C_4H_9		

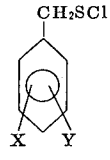
3-F	4-NO_2	
3-F	4C_2H_5	
2-Br	4-s-C_4H_9	
4-F	2-CH_3	
4-F	2-C_2H_5	
4-F	2-CH_3O	
4-F	3-C_2H_5O	
4-F	3-n-C_3H_7	
4-F	3-HO	
4-F	2-NO_2	
4-F	2-s-C_4H_9	
3-CH_3O	4-HO	
2-C_2H_5O	4-HO	
2-HO	4-i-C_3H_7O	
2-HO	4-C_2H_5	
2-Br	4-C_2H_5	
2-Br	3-CH_3	
2-Br	6-CH_3O	
2-Cl	6-CH_3O	
2-Cl	5-n-C_3H_7	
2-Cl	4-i-C_3H_7	
2-Cl	4-HO	
3-Cl	2-HO	
3-Cl	2-Br	
3-Cl	2-Cl	

4-Cl	2-i-C_3H_7
4-Cl	2-C_2H_5O
4-Cl	2-HO
4-Cl	3-HO
4-Cl	2-NO_2
4Cl	2-s-C_4H_9
2-Cl	4-s-C_4H_9

PREPARATION F

Benzenesulfenyl Chlorides

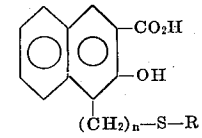
The following α-toluenesulfenyl chlorides, not previously reported in the chemical literature, are prepared from the corresponding thiols via chlorination according to the procedure as taught by Douglass, et al., J. Org. Chem., 26, 1966 (1961):



X	Y	X	Y
2- F	H	2-C_2H_5	H
3-F	H	4-C_2H_5	H
4-F	H	2-i-C_3H_7	H
2-Cl	H	3-t-C_4H_9	H
3-Cl	H	4-t-C_4H_9	H
4-Cl	H	4-n-C_4H_9	H
2-Br	H	2-n-C_4H_9	H
3-Br	H	4-s-C_4H_9	H
4-Br	H	2-CH_3O	H
2-CF_3	H	3-CH_3O	H
3-CF_3	H	4-CH_3O	H
4-CF_3	H	2-C_2H_5O	H
2-NO_2	H	2-Cl	6-Cl
3-NO_2	H	2-Cl	4-Cl
4-NO_2	H	2-Cl	6-Br
2-CH_3	H	2-Cl	4-Br
3-CH_3	H	3-Cl	5-Cl
4-CH_3	H	3-Cl	4-Cl
2-F	4-F	4-Cl	2-F
2-F	6-F	2-F	4-HO
2-Br	6-Br	2-F	3-HO
2-Br	4-Br	2-F	4-CH_3O
2-Cl	4-CF_3	2-F	4-n-C_4H_9
3-CF_3	5-Cl	3-F	4-CH_3O

What is claimed is:

1. A naphthoic acid selected from those of the formula:



and the sodium, potassium and ammonium salts and alkyl esters containing from one to four carbon atoms thereof, wherein:

R is selected from the group consisting of cycloalkyl containing from three to 10 carbon atoms; phenyl, benzyl and mono- and disubstituted phenyl and benzyl said substituents being selected from the group consisting of fluorine, chlorine, bromine, hydroxy, alkyl and alkoxy each containing from one to four carbon atoms, trifluoromethyl, amino and substituted amino said substituent being selected from the group consisting of alkyl and alkanoyl each containing from one to four carbon atoms, dialkyl each containing from one to four carbon atoms and phenylsulfonyl; naphthyl; pyridyl and thiazolyl; and

n is an integer of 0 or 1.

2. The compound of claim 1 wherein R is monosubstituted phenyl and *n* is 1.

3. 1-(o-Tolylthiomethyl)-2-hydroxy-3-naphthoic acid.

4. 1-(m-Tolylthiomethyl)-2-hydroxy-3-naphthoic acid.

5. 1-(p-Tolylthiomethyl)-2-hydroxy-3-naphthoic acid.

6. 1-(o-Chlorophenylthiomethyl)-2-hydroxy-3-naphthoic acid.

7. 1-(p-Chlorophenylthiomethyl)-2-hydroxy-3-naphthoic acid.

8. 1-(o-Bromophenylthiomethyl)-2-hydroxy-3-naphthoic acid.

9. 1-(m-Bromophenylthiomethyl)-2-hydroxy-3-naphthoic acid.

10. 1-(2,3-Dichlorophenylthiomethyl)-2-hydroxy-3-naphthoic acid.

11. 1-(2-Isopropylphenylthiomethyl)-2-hydroxy-3-naphthoic acid.

12. The compound of claim 1 wherein R is naphthyl and *n* is 1.

13. 1-(2-Naphthyl)-2-hydroxy-3-naphthoic acid.

14. A compound of claim 1 wherein R is phenyl and *n* is an integer of 0 or 1.

15. 1-Phenylthiomethyl-2-hydroxy-3-naphthoic acid.

16. A compound of claim 1 wherein R is substituted phenyl and *n* is 0.

17. 1-(o-Chlorophenylthio)-2-hydroxy-3-naphthoic acid.

* * * * *