

1

3,833,726

1-OXO-SUBSTITUTED-TETRAHYDRONAPHTHALENES (SUBSTITUTED-TETRALONES)

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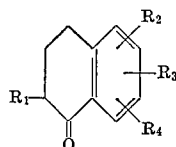
Int. Cl. C07c 49/80, 49/82

U.S. Cl. 260—590

9 Claims

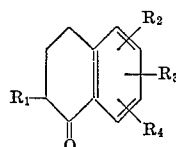
ABSTRACT OF THE DISCLOSURE

Compounds of the formula are disclosed:



wherein R₁ is hydrogen, hydroxymethylene, benzylidene or benzylidene substituted by halogen or nitro; R₂, R₃ and R₄ are hydrogen, alkyl, alkoxy, amino, acylamino, carboxy, carboxyalkyl, halogen, hydroxy, nitro, allyl and methanesulfonylamino. These compounds are useful in providing symptomatic relief in allergic conditions such as asthma, hay fever and the like.

The present invention is concerned with 1-oxo-substituted-tetrahydronaphthalenes (substituted-tetralones) having the following structural formula:



wherein R₁ is hydrogen, hydroxymethylene, benzylidene or benzylidene substituted by halogen or nitro; R₂, R₃ and R₄ are hydrogen, alkyl, alkoxy, amino, acylamino, carboxy, carboxyalkyl, halogen, hydroxy, nitro, allyl or methanesulfonylamino. The R₂-R₄ substituents are preferably substituted at the 5,6,7 or 8 position of the 3,4-dihydro-1(2H)-naphthalenone nucleus.

In the above definitions for R₂, R₃ and R₄, the term "alkyl" and the alkyl portion in terms such as alkoxy and carboxyalkyl is meant to encompass straight or branched chain alkyl groups having 1-6 carbon atoms. These include, for example, methyl, ethyl, propyl and the like.

The "acyl" portion of acylamino is meant to be the residue derived from an alkanic acid such as acetic, propionic, butyric and the like.

The term "halogen" includes all its four members, preferably chlorine.

These compounds form salts with pharmaceutically acceptable acids and bases. For example, they form acid addition salts with acids such as hydrochloric, sulfuric, nitric and the like and they form base addition salts with bases such as sodium hydroxide, potassium hydroxide and the like. These salts are also within the scope of this invention.

The above compounds exhibit anti-allergic activity in a mammalian host, e.g., cats, dogs, monkeys and the like. For example, these compounds are capable of protecting guinea pigs from histamine-induced reactions at a dose of 1 mg. to 100 mg./kg. orally or by injection.

The compounds of this invention are useful in alleviating or in providing symptomatic relief in allergic reactions such as hay fever, asthma, eczema and dermatitis. Generally speaking, a dose of 1 mg. to 100 mg./kg. of body

2

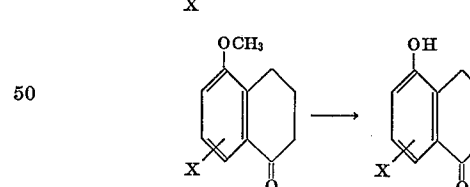
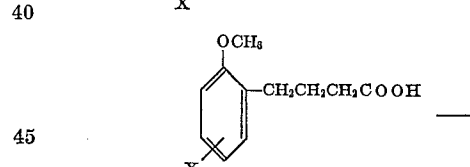
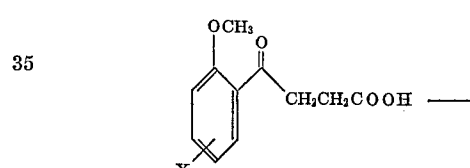
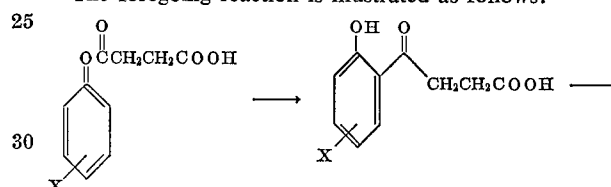
weight of the animal being treated orally or parenterally is required to achieve anti-allergic action.

In order to use these compounds they are combined with pharmaceutical excipients such as lactose, mannitol and compressed into dosage forms such as tablets.

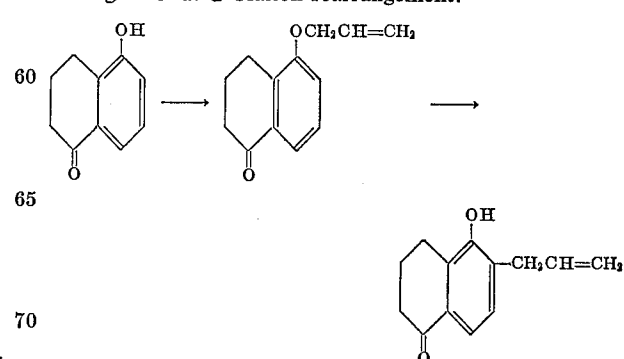
They can also be combined with parenteral vehicles such as water for injection, peanut oil or into dosage forms for parenteral administration.

According to this invention, these compounds are prepared as follows. First, an appropriate substituted phenylhydrogen succinate is subjected to a Fries rearrangement. The resulting β -(substituted-2-hydroxybenzoyl)propionic acid is methylated, using standard methylating agents such as dimethylsulfate. The methylated compound is subsequently reduced to the corresponding γ -(2-methoxyphenyl)butyric acid. Ring closure to the substituted 5-methoxytetralone is accomplished with condensing agents such as polyphosphoric acid, phosphorous oxychloride and the like. Alternatively, ring closure is effected by treating the acid chloride with aluminum chloride. Ether cleavage is accomplished either by refluxing the ether in a mixture of aluminum chloride and benzene or by fusion in pyridine hydrochloride.

The foregoing reaction is illustrated as follows:

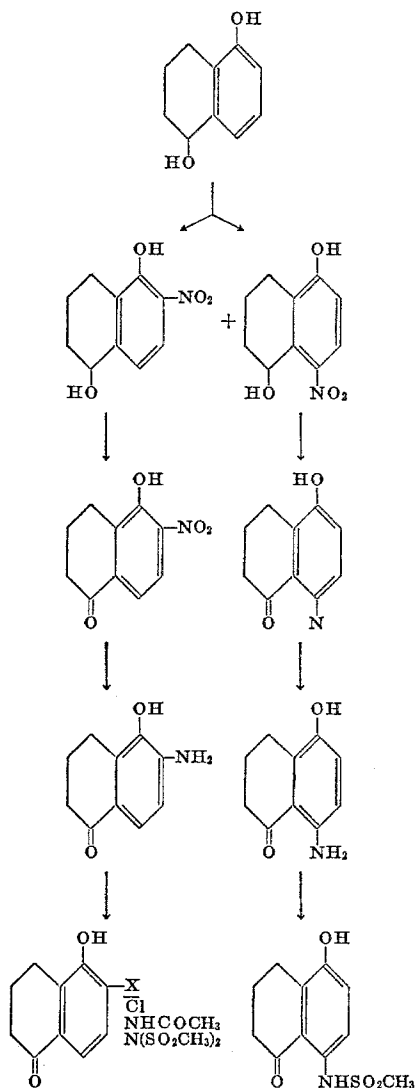


The 6-allyl-5-hydroxytetralone is obtained by the following illustrated Claisen rearrangement:



3

The other compounds of this invention are prepared in accordance with the following reaction scheme:



In order to further illustrate the practice of this invention, the following examples are included:

EXAMPLE 1

1,5 - Dihydroxy - 6-nitro-1,2,3,4-tetrahydronaphthalene and 1,5-Dihydroxy-8-nitro-1,2,3,4-tetrahydronaphthalene.—To a solution of 76.5 g. (467 mmol) of 1,5-dihydroxy-1,2,3,4-tetrahydronaphthalene⁹ in 750 ml. of glacial AcOH, H₂O (150 ml.) was added and the solution was cooled to 0° before 70% HNO₃ (59.0 ml.) was added. The HNO₃ was added slowly maintaining a reaction temperature below 15°. After 30 min., the reaction mixture was poured onto 5 l. ice-H₂O and extracted with CHCl₃ (2× 1.) and CH₂Cl₂ (1× 1.). An insoluble solid was collected by filtration and 10.4 g. (10.7%), m.p. 179–184° of homogeneous solid was obtained. The combined organic extracts were dried (MgSO₄) and evaporated *in vacuo* to give 74.2 g. (76.1%) of a brown, oily residue. This crude mixture of products was placed on an acid washed Al₂O₃ column (1 kg.) and eluted with

CHCl₃—MeOH

fractions of 500 ml. Homogeneous 6 - isomer was obtained from 1% MeOH—CHCl₃ eluate; yield 26.4 g. (27.0%). Analytically pure sample was obtained by recrystallization from EtOAc-hexane, m.p. 98–100°.

Anal.—Calcd. for C₁₀H₁₁NO₄: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.57; H, 5.42; N, 6.44.

4

The 8-isomeric product was obtained from the MeOH eluate and gave a total yield of 12.3 g. (13.0%), m.p. 179–184° when combined with solid recovered from the extraction. The analytical sample was obtained by recrystallization from MeOH—H₂O, m.p. 183–185°.

Anal.—Calcd. for C₁₀H₁₁NO₄: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.52; H, 5.42; N, 6.85.

EXAMPLE 2

3,4 - Dihydro - 5 - hydroxy-6-nitro-1(2H)-naphthalene.—To an acetone solution (250 ml.) containing 28.5 g. (136 mmol) of 6-nitro-1,5-dihydroxy-Tetralin, a mixture of 15.0 g. (150 mmol) of CrO₃ in H₂O (50 ml.) and H₂SO₄ (16.5 ml.) was added in a dropwise manner below 10°. The reaction was allowed to stir at 0° for 30 min. and poured onto ice-H₂O (2 l.). The solid which formed was collected by filtration, yield 26.3 g. (93.6%), m.p. 127–128°. The analytical sample was obtained by recrystallization from EtOAc-hexane, m.p. 130–131°.

Anal.—Calcd. for C₁₀H₉NO₄: C, 57.97; H, 4.38; N, 6.76. Found: C, 58.05; H, 4.56; N, 6.50.

EXAMPLE 3

3,4 - Dihydro - 5 - hydroxy-8-nitro-1(2H)-naphthalene.—A cold mixture of 3.30 g. (33.0 mmoles) of CrO₃, H₂SO₄ (3.7 ml.) and H₂O (12.5 ml.) was added dropwise to an acetone solution (100 ml.) of 5.78 g. (27.5 mmoles) of 8-nitro-1,5-dihydroxy-Tetralin maintained below 10°. The reaction mixture was stirred at 0° for an additional 30 min. before being poured onto 1 l. of ice-H₂O. The resultant solid was collected to give 4.42 g. (77.4%), m.p. 250–251° dec. The analytical sample was obtained by recrystallization from EtOAc-hexane, m.p. 254° dec.

Anal.—Calcd. of C₁₀H₉NO₄: C, 57.97; H, 4.38; N, 6.76. Found: C, 58.01; H, 4.46; N, 6.90.

EXAMPLE 4

6-Amino - 3,4 - dihydro-5-hydroxy-1(2H)-naphthalene Hydrochloride.—A suspension of 2.07 g. (10.0 mmol) of 6-nitro-5-hydroxytetralone in MeOH (150 ml.) was hydrogenated over 100 mg. of PtO₂ until the theoretical uptake of hydrogen was observed. The catalyst was removed by filtration after 10 ml. of 6N HCl had been added to the reaction mixture. The MeOH filtrate was evaporated and a solid product was obtained. The solid residue was recrystallized from 2-PrOH-MeOH and gave the analytically pure product; yield 1.15 g. (54.0%), m.p. 226–230° dec.

Anal.—Calcd. for C₁₀H₁₁NO₂·HCl: C, 56.21; H, 5.66; N, 6.56; Cl, 16.59. Found: C, 56.36; H, 5.83; N, 6.80; Cl, 16.47.

EXAMPLE 5

8-Amino - 3,4 - dihydro-5-hydroxy-1(2H)-naphthalene Hydrochloride.—A MeOH solution (200 ml.) containing 1.04 g. (5.02 mmol) of 8-nitro-5-hydroxytetralone was hydrogenated over PtO₂ (100 mg.) until the theoretical uptake of hydrogen had occurred. After 10 ml. of 6N HCl had been added to the reaction mixture, the catalyst was removed by filtration and evaporation of the MeOH filtrate gave the crude solid residue; yield 953 mg. (88.0%), m.p. 204–212° dec. Recrystallization of the crude material from 2-PrOH gave the analytical yellow salt, m.p. 211–213° dec.

Anal.—Calcd. for C₁₀H₁₁NO₂·HCl: C, 56.21; H, 5.66; N, 6.56; Cl, 16.59. Found: C, 56.51; H, 5.77; N, 6.80; Cl, 16.72.

EXAMPLE 6

5-Hydroxy - 6 - [N,N-dimethanesulfonyl]aminotetralone.—A mixture of CH₂Cl₂ (500 ml.), 100 ml. of triethylamine, 21.4 g. (100 mmoles) of 5-hydroxy-6-amino-tetralone and 20 ml. (256 mmoles) of methanesulfonyl chloride was heated at reflux for 2 hrs. The mixture was washed with H₂O (1× 500 ml.) and dried (MgSO₄) before being evaporated to give the N,O-trimethylsulfonyl

5

intermediate. The intermediate was then heated at reflux for 1 hr. in a mixture of MeOH (250 ml.) and 5% NaOH (250 ml.). The basic mixture was poured onto ice and acidified with 3N HCl. The precipitate which formed was collected by filtration to give a quantitative yield of the desired product, m.p. 175–180°. The analytical sample was obtained by recrystallization from 2-propanol; yield 12.0 g. (47.1%), m.p. 184–186°.

Anal.—Calcd. for $C_{12}H_{15}NO_6S_2$: C, 43.23; H, 4.54; N, 4.20; S, 19.24. Found: C, 43.23; H, 4.66; N, 4.23; S, 19.17.

EXAMPLE 7

6-Acetamido - 5 - hydroxy-1-tetralone.—To a suspension of 5.14 g. (24.1 mmoles) of 6-amino-5-hydroxy-1-tetralone hydrochloride in CH_2Cl_2 (100 ml.) was added Et_3N (140 mmoles) and acetyl chloride (70 mmoles). The mixture was heated at reflux for 1 hr., extracted with 6N HCl (1× 100 ml.), 5% $NaHCO_3$ (1× 100 ml.), H_2O (1× 100 ml.) and dried with $MgSO_4$ before being evaporated to give the 5-acetoxy-6-acetamidotetralone intermediate.

The desired product was obtained by heating the diacetyl intermediate in a mixture of MeOH (50 ml.) and 20% NaOH (50 ml.) for 1 hr. The reaction mixture was cooled, acidified and extracted with CH_2Cl_2 . The CH_2Cl_2 extract was dried ($MgSO_4$) and evaporated to give the 6-acetamido-5-hydroxytetralone; yield 4.98 g. (94%), m.p. 130–140°. The analytical sample was obtained by recrystallization from toluene, m.p. 146–147°.

Anal.—Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.69; H, 5.97; N, 6.54.

EXAMPLE 8

5-Hydroxy - 8 - methanesulfonamido-1-tetralone.—To a suspension of 4.27 g. (20 mmoles) of 5-hydroxy-8-amino-1-tetralone hydrochloride in 100 ml. of CH_2Cl_2 was added 180 mmoles of triethylamine and 100 mmoles of methanesulfonyl chloride. The resultant mixture was refluxed for 2 hrs. The reaction mixture was extracted with 6N HCl (2× 100 ml.), 5% $NaHCO_3$ solution (1× 100 ml.) and H_2O (1× 100 ml.). The CH_2Cl_2 solution was dried ($MgSO_4$) and evaporated to give the 5,8-dimethanesulfonyl intermediate.

The desired 5-hydroxy-8-methanesulfonamidotetralone was obtained by heating the 5,8-dimethanesulfonyl intermediate in a mixture of MeOH (50 ml.) and 10% NaOH (50 ml.) for 1½ hrs. The reaction mixture was poured onto ice- H_2O and acidified giving 3.23 g. (63.4%) of solid product, m.p. 195–200°. The analytical sample was obtained from 2-PrOH, m.p. 203–205°.

Anal.—Calcd. for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49; S, 12.56. Found: C, 51.92; H, 5.34; N, 5.61; S, 12.71, 12.81.

EXAMPLE 9

6,8-Dinitro-5-hydroxytetralone.—To 1.62 g. (10.0 mmoles) of 5-hydroxytetralone³ in 11.2 ml. of glacial acid heated at 50°, was added 2.4 ml. (40.0 mmoles) of 70% HNO_3 . The mixture was stirred at 50° for 1 hr. Cooling and addition of water (50 ml.) gave crude solid product; yield 2.0 g. (79.4%). The analytical sample was obtained from ethyl acetate by recrystallization; yield 1.55 g. (61.5%), m.p. 238–239°.

Anal.—Calcd. for $C_{10}H_8N_2O_8$: C, 47.62; H, 3.20; N, 11.11. Found: C, 47.61; H, 3.24; N, 11.26.

EXAMPLE 10

6-Allyl - 3,4 - dihydro - 5 - hydroxy-1(2H)-naphthalenone.—Allyl bromide (17.0 g., 140 mmol), anhydrous K_2CO_3 (19.3 g., 140 mmol) and 5-hydroxy-1-tetralone³ (20.0 g., 124 mmol) was refluxed for 21 hr. in dry Me_2CO . The reaction mixture was evaporated *in vacuo* and gave a residue which was dissolved in EtOAc (400 ml.). After washing the EtOAc solution with 5% NaOH (2× 400 ml.) and H_2O (1× 400 ml.), the EtOAc was

6

dried with $MgSO_4$ before being evaporated to give the crude 5-allyloxytetralone; yield 24.6 g. (97.5%).

The crude 5-allyloxytetralone (12.6 g., 61.8 mmol) was heated at reflux in diethylaniline (50 ml.) for 28 hr. The reaction mixture was poured into 20% NaOH (1 l.) and extracted with Et_2O (3× 1 l.). The basic phase was acidified with HCl and extracted with $CHCl_3$ (3× 1.5 l.). The $CHCl_3$ extracts were combined, dried ($MgSO_4$) and evaporated to give 7.20 g. (57.2%) of crude 21 which crystallized upon standing. The analytical sample was obtained by recrystallization from $phCH_3$ -hexane, m.p. 80–83°.

Anal.—Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.25; H, 7.04.

EXAMPLE 11

2-Benzylidene - 3,4 - dihydro-5-hydroxy-1(2H)-naphthalenone.—A mixture of 19.4 g. (120 mmol) of 5-hydroxytetralone³, 12.0 g. (300 mmol) of NaOH and 14.8 g. (140 mmol) of benzaldehyde was heated at reflux for 2 hrs. in 50% aqueous MeOH (100 ml.). The mixture was allowed to stir at room temperature overnight. The reaction mixture was acidified with 30 ml. of conc. HCl and poured onto ice- H_2O (500 ml.) giving the solid product; yield 26.1 g. (87.3%). The tan analytically pure product was obtained by recrystallization from EtOAc-hexane; yield 12.0 g. (40.0%), m.p. 168–171° dec.

Anal.—Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.38; H, 5.67.

EXAMPLE 12

2-(p-Chlorobenzylidene) - 3,4 - dihydro - 5 - hydroxy-1(2H)-naphthalenone.—Using the procedure outlined in the synthesis of 2-benzylidene-5-hydroxytetralone, a crude yield of 31.6 g. (92.2%), m.p. 217–220° was obtained from 19.4 g. (120 mmol) of 5-hydroxytetralone³ and 140 mmol of p-chlorobenzaldehyde. One recrystallization from MeOH- Et_2O gave the analytical sample, m.p. 229–231°.

Anal.—Calcd. for $C_{17}H_{13}ClO_2$: C, 71.71; H, 4.60; Cl, 12.45. Found: C, 71.87; H, 4.64; Cl, 12.19.

EXAMPLE 13

5 - Hydroxy-2-(p-nitrobenzylidene)tetralone.—A reaction mixture containing 6.51 g. (40.2 mmol) of 5-hydroxytetralone³, 7.56 g. (50.0 mmol) of p-nitrobenzaldehyde, 10 ml. of conc. H_2SO_4 and 50 ml. of glacial HOAc was allowed to react at room temperature for 72 hrs. The mixture was poured onto 500 ml. of ice- H_2O and 11.9 g. (100%) of 2-(p-nitrobenzylidene) - 5 - hydroxytetralone was obtained, m.p. 230–240°.

EXAMPLE 14

8-Chloro-5-hydroxytetralone.—Pyridine HCl (100 g.) was heated at 190° for 0.5 hr. and 20.0 g. (91.2 mmol) of 8-chloro-5-methoxytetralone² was added. The reaction temperature was maintained at 185–190° for 2.5 hrs. and then poured into H_2O (1500 ml.). The precipitate which formed was collected by filtration and gave 18.2 g. (97.8%) of homogeneous product, m.p. 225–228°. The analytical sample was obtained by recrystallization from toluene, m.p. 229–231°.

Anal.—Calcd. for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61; Cl, 18.03. Found: C, 61.14; H, 4.78; Cl, 18.05, 17.84.

EXAMPLE 15

6 - Chloro - 3,4 - dihydro - 5 - hydroxy-1(2H)-naphthalenone.—A solution of 8.28 g. (120 mmol) of $NaNO_2$ in 100 ml. of cold H_2O was added dropwise over 30 min. to a cooled suspension of 21.3 g. (100 mmol) of 6-amino-5-hydroxytetralone in 100 ml. of 6N HCl. The reaction mixture was stirred at 0° for 15 min. and a solution of 11.9 g. (60.0 mmol) of Cu_2Cl_2 in 100 ml. of 6N HCl was added dropwise. After the evolution of N_2 gas had ceased,

the reaction mixture was heated to boiling for 30 min. Cooling gave a solid which was collected by filtration to give 16.7 g. (84.8%), m.p. 95–110° of crude 36. The crude 36 was sublimed at 120°/2 min. and 7.40 g. (37.6%), m.p. 128–133° of the purified product was collected. The analytical sample was obtained by recrystallization from hexane, m.p. 133–135°.

Anal.—Calcd. for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61; Cl, 18.03. Found: C, 61.38; H, 4.68; Cl, 18.01.

EXAMPLE 16

3,4 - Dihydro-5-hydroxy - 8 - methyl-1(2H)-naphthalenone.—A mixture of freshly fused pyridine hydrochloride (5.00 g.) and 2.00 g. (10.5 mmol) of 3,4-dihydro-5 - methoxy - 8 - methyl-1(2H)naphthalenone⁷ was heated at 195–200° for 1.5 hr. Upon cooling the mixture, the material was poured onto 50 ml. of ice- H_2O and the solid which formed was collected by filtration; yield 1.79 g. (96.6%), m.p. 181–185°. One recrystallization of the solid from $PhCH_3$ gave the analytical sample, m.p. 188–190°.

Anal.—Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.25; H, 6.96.

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The reference numerals 1 through 9 are sources of starting material or the method of their preparation in the examples.

We claim:

1. A compound which is 3,4-dihydro-5-hydroxy-6-nitro-1(2H)-naphthalenone.
2. A compound which is 3,4-dihydro-5-hydroxy-8-nitro-1(2H)-naphthalenone.
3. A compound which is 6,8 - dinitro - 5 - hydroxy - 1-tetralone.
4. A compound which is 6-allyl-3,4-dihydro-5-hydroxy-1(2H)-naphthalenone.
5. A compound which is 2-benzylidene-3,4-dihydro-5-hydroxy-1(2H)-naphthalenone.
6. A compound which is 2-(p-chlorobenzylidene)-3,4-dihydro-5-hydroxy-1(2H)-naphthalenone.
7. A compound which is 5-hydroxy-2-(p-nitrobenzylidene)-1-tetralone.
8. A compound which is 8-chloro - 5 - hydroxy-1-tetralone.
9. A compound which is 6 - chloro-3,4-dihydro-5-hydroxy-1(2H)-naphthalenone.

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DANIEL D. HORWITZ, Primary Examiner

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260—485 H, 485 J, 519, 520, 556 A, 562 A, 575, 645, 469, 472, 473 F; 424—324, 330, 331