United States Patent

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[73] Assignee **Pfizer Inc.**

[54] **NOVEL 2-ARYL-1,3-INDANDIONES AND 2-ARYL-2,3-DIHYDROBENZ [F] INDENE-1,3-DIONES**
4 Claims, No Drawings

[52] **U.S. Cl.** ..... **260/590,** 260/511, 260/520, 260/556 AR, 260/562 P, 260/570.7, 260/578, 424/321, 424/324, 424/331
[51] **Int. Cl.** **C07c 49/80**
[50] **Field of Search** 260/590, 520, 578, 570.7, 562, 556, 511

[56] **References Cited**

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OTHER REFERENCES

Horton et al., Chem. Abstracts 54, 21002 (1960)
Lombardino et al., Chem. Abstracts 68, 858290 (1968)

Primary Examiner—Daniel D. Horwitz
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ABSTRACT: Novel 2-aryl-1,3-indandiones and 2-aryl-2,3-dihydrobenz [f] indene-1,3-diones and their use in lowering the blood lipid level in mammals.

NOVEL 2-ARYL-1,3-INDANDIONES AND 2-ARYL-2,3-DIHYDROBENZ [F] INDENE-1,3-DIONES

BACKGROUND OF THE INVENTION

This invention relates to novel 2-aryl-1,3-indandiones and 2-aryl-2,3-dihydrobenz[f]indene-1,3-diones and their use in lowering the blood lipid level in mammals.

Atherosclerosis, a form of arteriosclerosis, is characterized by internal thickening of the major blood vessels due to localized accumulation of lipids, of which cholesterol and other β-lipoproteins such as the tirglycerides comprise the major constituents. It has also been found that those suffering from the disease exhibit abnormally high blood cholesterol levels. While the etiology of the disease is not fully understood, it is believed that the β-lipoproteins, in particular cholesterol, play an important role in the disease.

In the advanced stages of the disease, plaques, comprising cholesterol and other β-lipoproteins, accumulate in the aorta coronary, cerebral, and peripheral arteries of the lower extremities. As these plaques increase in size, the danger of fibrin deposition, possibly resulting in thrombosis and occlusion, is enhanced.

While no established method has been found for preventing atherosclerosis, it has been recommended that dietary habits be observed that will ensure low β-lipoprotein levels. Besides stringent dietary management, various therapeutic agents such as estrogens, thyroxine analogs and sitosterol preparations have been used to lower the cholesterol levels of those afflicted with the condition.

It has now been found that various 2-aryl-1,3-indandiones and 2-aryl-2,3-dihydrobenz[f]indene-1,3-diones are effective hypolipemic agents because of their ability to lower the blood lipid level of mammals. Consequently, these compounds can be expected to be useful in the treatment of atherosclerosis and related cardiovascular disease which are associated with elevated blood lipid levels.

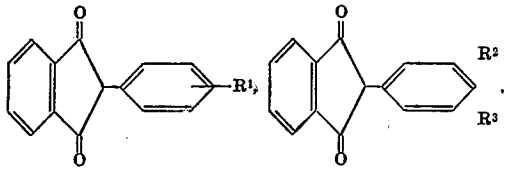
We have also found that some of the compounds described herein also possess a high degree of anti-inflammatory activity in mammals and are effective in preventing and inhibiting the formation of granulomatous tissue. Consequently, these particular compounds are expected to be of value in the treatment of those arthritic disorders that are responsive to the administration of anti-inflammatory agents.

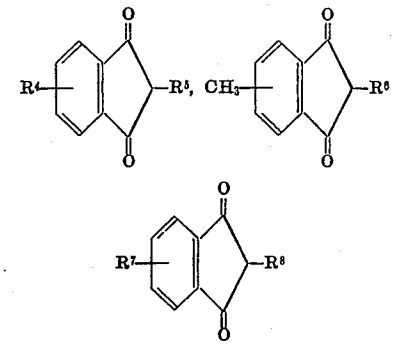
Although some 2-aryl-1,3-indandiones have been reported in the prior art to exhibit anti-inflammatory activity, many of them also inhibit blood coagulation. Indeed, 2-aryl-1,3-indandiones have been used in man as anticoagulants, e.g., 2-phenyl-1,3-indandione. Nevertheless, the use of anticoagulants is associated with a considerable amount of risk. Such compounds can cause fatal hemorrhaging even when average dosage levels are employed. In this respect, it should be noted that some of these compounds have even been used as pesticides, e.g., 2-pivalyl-1,3-indandione (Pival) is used as a rodenticide. Accordingly, it would not be desirable to employ a 2-aryl-1,3-indandione for a therapeutic use if in addition it also inhibits the coagulation of blood, i.e., inhibits prothrombin synthesis.

The present invention describes a series of 2-aryl-1,3-indandiones and 2-aryl-2,3-dihydrobenz[f]indene-1,3-diones which lower the blood lipid level in mammals without exhibiting the objectionable property of inhibiting the coagulation of blood. Further, some of the novel compounds of the instant invention are also effective anti-inflammatory agents and have been described in J. Med. Chem., 11, 342 (1968).

SUMMARY OF THE INVENTION

This invention comprises a series of novel 2-aryl-1,3-indandiones having the formulas:





where

R^1 is —OH, —NH_2, —OCH_2CO_2H, —$NHCOCH_3$, $(C_2H_5)_2NCH_2CH_2O$—, —CF_3, or —SO_2CF_3.

R^2 and R^3 are CH_3O—, —OH, —SO_3Na, or $(CH_3)_2NSO_2$; provided that R^2 and R^3 are not both —OCH_3.

R^4 is —Br, —NO_2, —CF_3, or —NH_2.

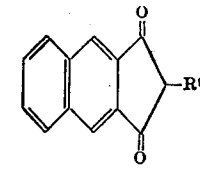
R^5 is methoxyphenyl, bromophenyl, trifluoromethylphenyl trifluoromethylsulfonylphenyl, or 2-naphthyl.

R^6 is methoxyphenyl, 3′-chlorophenyl, bromophenyl, trifluoromethylsulfonylphenyl, or 2-naphthyl.

R^7 is —NO_2 or CF_3; and

R^8 is o-, m-, and p-tolyl

This invention also comprises a series of 2-aryl-2,3-dihydrobenz[f]indene-1,3-diones having the formula:



where R^9 is tolyl, bromophenyl, iodophenyl, trifluoromethylphenyl, methoxyphenyl, trifluoromethylsulfonylphenyl, or 2-naphthyl.

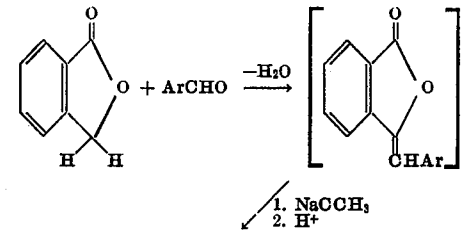
The novel compounds of the present invention effectively lower the blood lipid level in mammals and are expected to be useful in the treatment of atherosclerosis and related cardiovascular diseases which are associated with elevated blood lipid levels. Some of these compounds also exhibit anti-inflammatory activity and are expected to be of value in the treatment of those arthritic disorders that are responsive to the administration of anti-inflammatory agents.

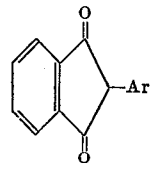
Furthermore, unlike many of the known compounds in the 2-aryl-1,3-indandione series, the compounds of the present invention do not have the objectionable property of inhibiting prothrombin synthesis.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of the present invention can be prepared by three previously described procedures. Of the greatest utility for preparing analogs with no substituents in the indane ring is the method of S. L. Shapiro, K. Geiger, J. Youlus and L. Freedman, J. Org. Chem., 26, 3580 (1961), which is outlined in Chart I.

CHART I

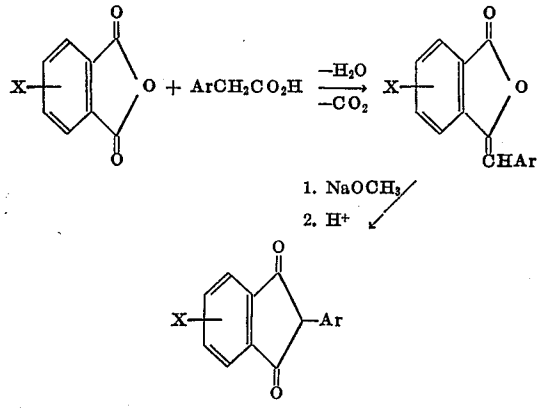




In this synthetic scheme, a solution of sodium methoxide in methanol is added to a mixture of benzaldehyde and phthalide contained in anhydrous ethyl propionate. The resultant mixture is stirred at about 55° C. for 2 hours, cooled, and the solvent removed. The residue is dissolved in water and the resultant solution extracted with ether. Acidification of the aqueous phase provides the 2-aryl-1,3-indandione, which is separated and recrystallized from an appropriate solvent.

Since substituted phthalic acids are more readily accessible than substituted phthalides, a second preparative method was used which involves the condensation of an arylacetic acid with a substituted phthalic anhydride followed by rearrangement of the condensation product in sodium methoxide solution. The synthetic scheme is outlined below in Chart II.

CHART II

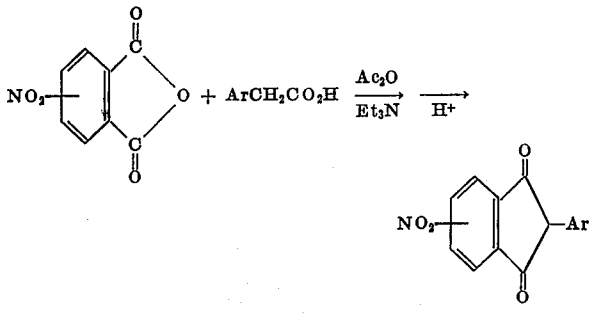


X=Br, CF_3, and CH_3.

In this procedure the appropriately substituted phthalic anhydride and arylacetic acid are heated together under nitrogen with anhydrous sodium acetate at 270°–275° C. for several hours. The crude condensation product is rearranged in methanol containing sodium methoxide, the reaction mixture evaporated to dryness, and the residue dissolved in water and the resultant solution extracted several times with ether. The aqueous phase is acidified and the 2-aryl-1,3-indandione that separates is collected and recrystallized from an appropriate solvent. This procedure is also used to prepare the 2-aryl-2,3-dihydrobenz[f]indene-1,3-diones.

With the 3- and 4-nitrophthalic anhydrides, the milder procedure of V. Oskaja and G. Vanays reported in Latvijas PSR Zinatnu Akad. Vestis, No. 6, 57 (1961); Chem. Abstr., 56, 5895 (1962); ibid., No. 1, 81 (1962); Chem. Abstr., 59, 7439 (1963), which is outlined in Chart III, is used.

CHART III



A mixture of the nitrophthalic anhydride, phenylacetic acid, acetic anhydride, and triethylamine is warmed on a steam bath, cooled and poured onto a mixture of ice and concentrated hydrochloric acid. The product is separated, dissolved in aqueous sodium hydroxide, and the resultant solution washed with ether. The aqueous phase is acidified and the 2-aryl-1,3-indandione is separated and recrystallized from an appropriate solvent.

Most of the phthalic anhydrides, arylacetic acids, and benzaldehydes used as starting materials in the preparation of the novel compounds of the present invention have either been reported in the prior art, or are readily synthesized by conventional procedures well known to those skilled in the art.

Almost all of the indandiones are isolated as their enol form, as evidenced by their deep red-violet color. Following recrystallization from polar solvents such as ethanol, the IR spectra (KBr) of most of these compounds exhibits a single carbonyl absorption band near 6.0μ and the UV spectra determined in methanol or methanol-sodium hydroxide solution are superimposable. See S. L Shapiro, K. Geiger and L. Freedman, J. Org. Chem., 25, 1860 (1960). It is interesting to note that the parent 2-phenyl-1,3-indandione is a white compound and shows two carbonyl absorption bands at 5.73 (m) and 5.81μ (s), indicative of the diketo form.

While the compounds of the present invention are named and depicted as 1,3-diones, it is to be understood that the corresponding enols and keto-enol equilibrium mixtures are embraced within the classification scheme used herein. As previously mentioned, the novel compounds of the present invention are effective hypolipemic agents, i.e., they lower the blood lipid level of mammals. This property has been dramatically demonstrated in rats. Groups, each comprising four animals, of normal Sprague-Dawley (Charles River) male rats weighing from 160 to 220 g. are fed rat chow containing 0.25 percent of the compounds described herein for two overnight feeding periods. On the morning of the third day the animals are anesthetized and bled from the abdominal aorta. The total plasma cholesterol is then determined by the method of J. J. Carr and I. J. Drekter reported in Clin. Chem., 2, 353 (1956). The plasma cholesterol level of the treated animals is found to be significantly reduced, when compared to animals not receiving the test compound.

The ability of the herein described compounds to lower the blood triglyceride level is illustrated by administering the compounds to dogs. A dosage level of 50 mg./kg. of the compound, in gelled capsules, is administered to dogs twice a day. This treatment is continued over a period of 2 weeks and on every second day, the cholesterol and triglyceride blood levels are determined. The cholesterol level is determined by the method given above, and the triglyceride level is measured by the method of E. Van Handel and D. B. Zilversmith, reported in J. Lab. & Clin. Med., 50, 152 (1957).

Comparison of the blood triglyceride levels of dogs receiving the test compounds shows a significant reduction as compared to the triglyceride levels of untreated animals.

For oral administration in capsule form, the preferred excipients are lactose and high-molecular weight polyethylene glycols. When aqueous suspensions are desired, the essential active ingredients are combined with emulsifying ingredients and/or suspending agents. Diluents such as ethanol, propylene glycol, glycerine and various combinations of diluents are employed.

A typical human dosage form for oral administration is as follows:

2-aryl-1,3-indandione	250 mg.
corn starch, dry	17.50 mg.
lactose	163.50 mg.
magnesium stearate	17.10 mg.
sodium lauryl sulfate	1.90 mg.

The compounds described herein can be administered parenterally as well as orally. For parenteral administration, solutions of the active ingredients in combination with other solutes such as glucose or saline are used. Such aqueous solu-

tions should be suitably buffered, if necessary, to render them isotonic.

The dosage required to lower the blood lipid level will be determined by the nature and the extent of the symptoms. Generally, small dosages will be administered initially with a gradual increase in 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 smaller quantity administered parenterally. In general, from about 50 to 500 mg. of active ingredient per kilogram of body weight administered in single or multiple dosage units significantly lowers the blood lipid level. In general, when administered to humans orally or parenterally, the effective average daily dose is suitably between about 0.3 and 3.0 g. per day.

As previously mentioned, the compounds of the present invention do not have the objectionable property of inhibiting prothrombin synthesis, i.e., they are not anticoagulants.

Inhibition of prothrombin synthesis was measured in rats after oral administration of 2 doses (100 mg./kg.) of drug in aqueous solution 8 hours apart and also after 9 doses (100 mg./kg.) 8 hours apart. Sixteen hours after the last dose, blood samples were drawn into oxalated syringes from the descending aorta while the animals were maintained under light pentobarbital anesthesia. Plasma was separated by centrifugation, and prothrombin time was determined automatically with a Model 202 Clot Timer (Mechrolab Inc.) using thromboplastin extract (Simplastin, Warner-Chilcott, Morris Plains, N.J.) as directed by the manufacturer.

In table I are listed some of the data obtained with known compounds in the series as well as data obtained for some of the novel compounds of the present invention.

TABLE I

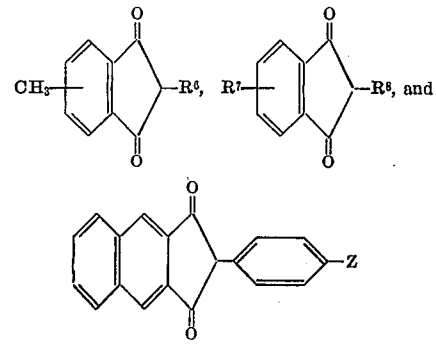
Compound	Prothrombin Time in Rats[a]
1. 2-phenyl-1,3-indandione	++
2. 2-(1'-naphthyl)-1,3-indandione	+
3. 2-(4'-methoxyphenyl)-1,3-indandione	++
4. 2-(3'-chlorophenyl)-1,3-indandione	++
5. 2-(4'-nitrophenyl)-1,3-indandione	++
6. 2-phenyl-5-bromo-1,3-indandione	++
7. 2-phenyl-5-nitro-1,3-indandione	++
8. 2-(3'-nitrophenyl)-1,3-indandione	–
9. 2-(2'hydroxyphenyl)-1,3-indandione	–
10. 2-(4'-acetamidophenyl)-1,3-indandione	–
11. 2-(4'-hydroxyphenyl)-1,3-indandione	–
12. 2-(3'-methoxyphenyl)-5-methyl-1,3-indandione	–
13. 2(2'naphthyl)-5-bromo-1,3-indandione	–
14. 2-(3'-trifluoromethylphenyl)-4-nitro-1,3-indandione	–
15. 2-(2'-naphthyl)-5-trifluoromethyl-1,3-indandione	–

[a]+, prolongation of prothrombin time 16 hours after administration of nine oral doses, 8 hours apart (100 mg./kg. po); ++, prolongation of prothrombin time 16 hours after administration of two oral doses, 8 hours apart (100 mg./kg. po); –, no porlongation of prothrombin time after nine oral does (100 mg./kg. po).

Compounds 1–7 listed in table I have been previously described in the prior art and all of them have the undesirable property of inhibiting prothrombin synthesis. On the other hand, compounds 8–15, now described for the first time, do not inhibit prothrombin synthesis after oral administration. Unlike many of the known compounds in the 2-aryl-1,3-indandione series, none of the novel compounds of the present invention inhibit prothrombin synthesis, thereby making them unobjectionable for therapeutic use.

As previously mentioned, some of the novel compounds of the present invention also exhibit anti-inflammatory activity as well as the aforementioned hypolipemic activity.

Listed below are the particular compounds that exhibit anti-inflammatory activity:



where R^6 is methoxyphenyl, 3'-chlorophenyl, bromophenyl, trifluoromethylsulfonylphenyl or 2-naphthyl;
R^7 is $-NO_2$ or $-CF_3$; and
R^8 is o-, m-, and p-tolyl;
Z is CF_3 or CF_3SO_2—;
2-(3'-nitrophenyl)-1,3-indandione
2-(3'-methoxyphenyl)-5-methyl-1,3-indandione
2-(2'naphthyl)-5-bromo-1,3-indandione
2-(3'-methylphenyl)-5-trifluoromethyl-1,3-indandione
2-(2'-naphthyl)-5-trifluoromethyl-1,3-indandione.

The anti-inflammatory activity of these compounds is determined by the inhibition of edema formation in the hind paw of rats (Charles River Strain; average weight 170 g.) in response to a subplantar injection of carrageenin ("rat-foot edema test"). The experimental procedures followed are those of Winter et al., as reported in Proc. Soc. Exp. Biol, N.Y., 111, 544 (1962) and J. Pharmacol, Exp. Therap., 141, 369 (1963).

In this test, unanesthetized adult male albino rats of 150 g. to 190 g. body weight are numbered, weighed, and an ink mark placed on the right lateral malleolus. Each paw is immersed in mercury exactly to the ink mark. The mercury is contained in a glass cylinder, connected to a Statham Pressure Transducer. The output from the transducer is fed through a control unit to a microvoltameter. The volume of mercury displaced by the immersed paw is read. Drugs are given by gavage. One hour after drug administration, edema is induced by injection of 0.05 ml. of 1 percent solution of carrageenin into the plantar tissue of the marked paws. Immediately thereafter, the volume of the injected foot is measured. The increase in foot volume 3 hours after the injection of carrageenin constitutes the individual response. The increase in volume of the feet of drug-treated animals are compared with those just receiving vehicle alone. The results obtained for some of the compounds of the present invention are tabulated in table II.

TABLE II

Rat Foot Edema Test

Compound	Inhibition of Edema Formation as Compared with Untreated Subjects[a]
2-(3'-nitrophenyl)-1,3-indandione	+
2-(3'-methoxyphenyl)-5-methyl-1,3-indandione	+
2-(2'-bromophenyl)-5-methyl-1,3-indandione	++
2-(2'-naphthyl)-5-bromo-1,3-indandione	++
2-(3'-trifluoromethylphenyl)-5-bromo-1,3-indandione	++
2-(3'-trifluoromethylphenyl)-5-nitro-1,3-indandione	++
2-(3'-methylphenyl)-5-nitro-1,3-indandione	+
2-(3'-trifluoromethylphenyl)-2,3-dihydro-benz[f]indene-1,3-dione	+

2-(3'-trifluoromethylphenyl)-5-trifluoromethyl-1,3-indandione	+
2-(2'-naphthyl)-5-trifluoromethyl-1,3-indandione	+
2-(3'-methylphenyl)-5-trifluoromethyl-1,3-indandione	+++
2-(3'-methoxyphenyl)-5-trifluoromethyl-1,3-indandione	++
2-(3'-bromophenyl)-5-trifluoromethyl-1,3-indandione	+

[a] Anti-inflammatory activity is reported as a mean inhibition of edema in the treated animals within the range of 0.5–1.5 times that of the mean inhibition of concurrently treated animals receiving aspirin (100 mg./kg. po); +, drug given at 100 mg./kg.; ++, drug given at 33 mg./kg.; +++, drug given at 10 mg./kg. po.

As can be seen by examination of table II, some of the novel compounds of the present invention are effective anti-inflammatory agents and, as previously mentioned, have the further pharmacological advantage of not inhibiting prothrombin synthesis. These compounds are expected to be useful in alleviating the swelling and inflammation exhibited by arthritic and rheumatic subjects. They can be administered either alone or in combinations with pharmaceutically acceptable carriers. The proportion of active ingredient to carrier is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice. For oral administration in capsule form, preferred excipients are lactose and high-molecular weight polyethylene glycols. When aqueous suspensions are desired, the essential active ingredients are combined with emulsifying and/or suspending agents. Diluents such as ethanol, propylene glycol, glycerine and various combinations of diluents are employed. For parenteral administration, solutions of the active ingredients in combination with other solutes such as glucose or saline are used. Such aqueous solutions should be suitably buffered, if necessary, to render them isotonic.

The dosage required to reduce inflammation and swelling in arthritic and rheumatic subjects will be determined by the nature and the extent of the symptoms. Generally, small dosages will be administered initially with a gradual increase in 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 smaller quantity administered parenterally. In general, from about 1 to 100 mg. of active ingredient per kilogram of body weight administered in single or multiple dosage units effectively reduces inflammation and swelling in arthritic and rheumatic subjects.

The following examples are provided to more fully illustrate the present invention, but are not to be construed as limiting the scope thereof in any way.

EXAMPLE I

To a mixture of 1 mole of 3-nitrobenzaldehyde, 1 mole of phthalide, and 480 ml. of dry ethyl propionate is rapidly added 3 moles of sodium methoxide in 700 ml. of methanol. The reaction mixture is stirred at 65° C. for 2 hours, cooled, and the solvent removed under reduced pressure. The residue is dissolved in 5.5 liters of water and the mixture extracted with ether and filtered. The filtrate is acidified to a pH of about 2 and the 2-(3'-nitrophenyl)-1,3-indandione is filtered and recrystallized from methyl ethyl ketone. The yield is 49 percent; m.p. 224°–226° C.

Anal. Calc'd for $C_{15}H_9NO_4$:		C, 67.40;	H, 3.39;	N, 5.24.
	Found:	C, 67.58;	H, 3.64;	N, 5.19.

Using the appropriate starting materials, the compounds in table III are also prepared according to the above procedure.

TABLE III

2-aryl-1,3-indandione	Crystallization solvent	Yield, percent	M.P., ° C.
2-(4'-carboxymethoxyphenyl)-1,3-indandione.	Ethanol	64	198.5–200.5
2-(4'-β-dimethylaminoethoxyphenyl)-1,3-indandione.	do	78	[1] 230–232
2-(4'-acetamidophenyl)-1,3-indandione.	do	54	239–241
2-(4'methoxy-3'-sodium sulfophenyl)-1,3-indandione.	do	9	286–288
2-(4'-methoxy-3'-dimethylsulfamylphenyl)-1,3-indandione.	do	15	185.5–187.5

[1] Decomposition.

EXAMPLE II

A. 2-(2'-methoxyphenyl)-1,3-indandione is prepared according to the procedure of example I from the appropriate starting materials. Yield: 71 percent; crystals from ethanol, m.p. 170.5°–172.5° C.

Anal. Calc'd for $C_{16}H_{12}O_3$:	C, 76.18;	H, 4.80.	
Found:	C, 76.17	H, 4.78	

B. A solution of 1.0 g. (0.004 moles) of 2-2'-methoxyphenyl)-1,3-indandione is refluxed in 25 ml. of 48 percent HBr acid for 3½ hours. After cooling, the dark red solids are filtered and recrystallized from a small amount of ethanol to yield 2-(2'-hydroxyphenyl)-1,3-indandione. Yield: 0.34 g. (39 percent); m.p. 218°–223° C.

Anal. Calc'd for $C_{15}H_{10}O_3$:	C, 75.62;	H, 4.23.	
Found:	C, 75.58;	H, 4.42.	

EXAMPLE III

A. 2-(4'-methoxyphenyl)-1,3-indandione is prepared according to the procedure of example I from the appropriate starting materials. M.p. 154°–155.5° C.

B. 2-(4'-hydroxyphenyl)-1,3-indandione is prepared from 2-(4'-methoxyphenyl)-1,3-indandione according to the procedure of example IIB. Yield: 64 percent; crystals from methanol, m.p. 259°–260° C.

Anal. Calc'd for $C_{15}H_{10}O_3$:	C, 75.62;	H, 4.23.	
Found:	C, 75.93;	H, 4.28.	

EXAMPLE IV

A. 2-(3',4'-dimethoxyphenyl)-1,3-indandione is prepared according to the method of example I from the appropriate starting materials. Yield: 65 percent; crystals from ethanol, m.p. 190.5°–192.5° C.

Similarly, using the appropriate starting materials the following compounds are also prepared:

2-(3'-carboxymethoxyphenyl)-1,3-indandione
2-(3'-β-dimethylaminoethoxyphenyl)-1,3-indandione
2-(2'-acetamidophenyl)-1,3-indandione
2-(3'-acetamidophenyl)-1,3-indandione
2-(3'-trifluoromethylphenyl)-1,3-indandione
2-(4'-trifluoromethylphenyl)-1,3-indandione
2-(3'-trifluoromethylsulfonylphenyl)-1,3-indandione
2-(4'-trifluoromethylsulfonylphenyl)-1,3-indandione
2-(4'-hydroxy-3'-sodium sulfophenyl)-1,3-indandione
2-(3'-hydroxy-4'-dimethylsulfamylphenyl)-1,3-indandione
2-(3', '-di sodium sulfophenyl)-1,3-indandione
2-(3'-dimethylsulfamyl-4-sodium sulfophenyl)-1,3-indandione
2-(3',4'-di-dimethylsulfamylphenyl)-1,3-indandione
2-(3'-methoxy-4'-sodium sulfophenyl)-1,3-indandione
2-(3'-methoxy-4'-dimethylsulfamylphenyl)-1,3-indandione

B. 2-(3',4'-dihydroxyphenyl)-1,3-indandione is prepared from 2-(3',4'-dimethoxyphenyl)-1,3-indandione according to the procedure of example IIB. B. Yield: 11 percent; crystals from acetic acid-water, m.p. 252°–254° C.

Anal. Calc'd for $C_{15}H_{10}O_4$:	C, 70.97;	H, 3.96.	
Found:	C, 70.97	H, 4.14.	

EXAMPLE V

A suspension of 2.8 g. (0.010 moles) of 2-(4'-acetamidophenyl)-1,3-indandione is refluxed in 100 ml. of 6N HCl for 4 hours. After filtration, the collected solids are dissolved in aqueous sodium hydroxide and the red solution is acidified with acetic acid to a pH of 6. The red precipitate is filtered and recrystallized from ethanol to give 0.76 g. (28 percent) of 2-(4'-aminophenyl)-1,3-indandione; m.p. 227°–229° C.

Anal. Calc'd for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67.
Found: C, 76.20; H, 4.80.

EXAMPLE VI

0.10 moles of 2-(3',4'-dihydroxyphenyl)-1,3-indandione is dissolved in about 300 ml. of a 1-molar sodium hydroxide solution and 0.10 moles of dimethyl sulfate is slowly added with stirring. The solution is stirred at about 50° C. for one-half hour, cooled, filtered and acidified to a pH of about 2 with hydrochloric acid. The mixture of 2-(3'-hydroxy-4'-methoxyphenyl)-1,3-indandione and 2-(3'-methoxy-4'-hydroxyphenyl)-1,3-indandione is separated and purified by column chromatography on silica gel or alumina.

EXAMPLE VII

4-Bromophthalic anhydride is prepared by refluxing a solution of 3.7 g. (0.015 moles) of 4-bromophthalic acid for 2 hours in 50 ml. of acetic anhydride containing 1 drop of sulfuric acid, followed by evaporation of the mixture to dryness. To the crude anhydride is added 2.8 g. (0.015 moles) of 2-naphthylacetic acid and 50 mg. of anhydrous sodium acetate. The solid mixture is heated under nitrogen at 275° C. for 2 hours. Upon cooling, a brown solid is obtained which is triturated with 10 percent sodium bicarbonate and dried under vacuum. The dried cure solid is rearranged in 100 ml. of refluxing methanol containing 2.1 g. (0.039 moles) of sodium methoxide. After 1 hour, the reaction mixture is evaporated to dryness and the residue dissolved in water. The aqueous solution is extracted several times with ether and the aqueous layer is acidified with 6N HCl acid. The crude red precipitate of 2-(2'-naphthyl)-5-bromo-1,3-indandione is recrystallized from ethanol to yield 2.5 g. of product (47 percent); m.p. 180.5°–181.5° C.

Anal. Calc'd for $C_{19}H_{11}BrO_2$: C, 64.97; H, 3.16.
Found: C, 64.63; H, 3.26.

Using the above procedure and the appropriate starting materials, 2-(3'-trifluoromethylphenyl)-5-bromo-1,3-indandione is similarly prepared in 27 percent yield; m.p. 154°–15 5.5° C. (ethanol).

Anal. Calc'd for $C_{16}H_8BrF_3O_2$: C, 52.06; H, 2.18.
Found: C, 51.86; H, 2.17.

Similarly, the following compounds are prepared from the appropriate starting materials:

2-(4'-methoxyphenyl)-5-bromo-1,3-indandione
2-(3'-methoxyphenyl)-5-bromo-1,3-indandione
2-(2'-bromophenyl)-5-bromo-1,3-indandione
2-(4'-trifluoromethylsulfonylphenyl)-5-bromo-1,3-indandione
2-(3'-trifluoromethylsulfonylphenyl)-5-bromo-1,3-indandione

3-Bromophthalic anhydride is prepared from 3-bromophthalic acid by the above procedure and used to prepare the compounds below:

2-(2'-naphthyl)-4-bromo-1,3-indandione
2-(3'-trifluoromethylphenyl)-4-bromo-1,3-indandione
2-(4'-methoxyphenyl)-4-bromo-1,3-indandione
2-(3'-methoxyphenyl)-4-bromo-1,3-indandione
2-(2'-bromophenyl)-4-bromo-1,3-indandione
2-(4'-trifluoromethylsulfonylphenyl)-4-bromo-1,3-indandione
2-(3'-trifluoromethylsulfonylphenyl)-4-bromo-1,3-indandione

EXAMPLE VIII

A solution of 0.05 moles of 3-nitrophthalic anhydride, 0.05 moles of 3-trifluoromethylphenyl acetic acid, 1.8 moles of acetic anhydride, and 0.15 moles of triethylamine is warmed on a steam bath for 15 minutes. After cooling, the reaction mixture is poured onto a mixture of ice and concentrated hydrochloric acid. The resultant gummy solid is separated, dissolved in aqueous sodium hydroxide, and the resultant solution washed with ether. The cooled aqueous layer is acidified with 6N hydrochloric acid and stirred at 0° C. to provide crude 2-(3'-trifluoromethylphenyl)-4-nitro-1,3-indandione in 19 percent yield; m.p. 174°–176.5° C. (ethanol).

Anal. Calc'd for $C_{16}H_8F_3NO_4$: C, 57.20; H, 2.40.
Found: C, 57.50; H, 2.77.

Using the appropriate starting materials, the following compounds are similarly prepared.

2-(3'-methoxyphenyl)-4-nitro-1,3-indandione
2-(4'-methoxyphenyl)-4-nitro-1,3-indandione
2-(2'-bromophenyl)-4-nitro-1,3-indandione
2-(4'-bromophenyl)-4-nitro-1,3-indandione
2-(3'-trifluoromethylsulfonylphenyl)-4-nitro-1,3-indandione
2-(2'-naphthyl)-4-nitro-1,3-indandione
2-(3'-methylphenyl)-4-nitro-1,3-indandione
2-(4'-methylphenyl)-4-nitro-1,3-indandione

Using 5-nitrophthalic anhydride in the above reaction instead of 4-nitrophthalic anhydride, the compounds in table IV are prepared from the appropriately substituted phenylacetic acids:

TABLE IV

2-aryl-1,3-indandione	Crystallization solvent	Yield, percent	M.P., ° C.
2-(3'-trifluoromethylphenyl)-5-nitro-1,3-indandione.	Isopropyl alcohol.	12	190.5–191.5
2-(3'-methylphenyl)-5-nitro-1,3-indandione.	Ethanol	21	188.5–190.5
2-(2'-naphthyl)-5-nitro-1,3-indandione			208–210

Likewise, the following compounds are also prepared:

2-(4'-methoxyphenyl)-5-nitro-1,3-indandione
2-(3'-bromophenyl)-5-nitro-1,3-indandione
2-(4'-trifluoromethylsulfonylphenyl)-5-nitro-1,3-indandione

EXAMPLE IX

Dry nitrogen is bubbled into a solution of 0.01 moles of 2-(3'-trifluoromethylphenyl)-4-nitro-1,3-indandione in 150 ml. of absolute ethanol. After the addition of 0.045 moles of hydrazine hydrate, a small portion of fresh Raney nickel catalyst is added. After stirring the reaction mixture for about 20 minutes at room temperature, a second portion of catalyst is added. After an additional hour, excess catalyst is added and the mixture is heated to boiling and filtered while hot. Acidification of the filtrate with 6N hydrochloric acid and addition of water provides crude 2-(3'-trifluoromethylphenyl)-4-amino-1,3-indandione, which is crystallized from ethanol.

Using the appropriate starting materials the following compounds are similarly prepared:

2-(3'-methoxyphenyl)-4--amino-1,3-indandione
2-(4'-methoxyphenyl)-4-amino-1,3-indandione
2-(2'-bromophenyl)-4-amino-1,3-indandione
2-(4'-bromophenyl)-4-amino-1,3-indandione
2-(3'-trifluoromethylsulfonylphenyl)-4-amino-1,3-indan-

dione
2-(2'-naphthyl)-4-amino-1,3-indandione
2-(3'-methylphenyl)-4-amino-1,3-indandione
2-(4'-methylphenyl-4-amino-1,3-indandione
2-(3'-trifluoromethylphenyl)-5-amino-1,3-indandione
2-(3'-methylphenyl)-5-amino-1,3-indandione
2-(2'-naphthyl)-5-amino-1,3-indandione
2-(4'-methoxyphenyl)-5-amino-1,3-indandione
2-(3'-bromophenyl)-5-amino-1,3-indandione
2-(4'-trifluoromethylsulfonylphenyl)-5-amino-1,3-indandione

EXAMPLE X

4-trifluormethylphthalic anhydride is prepared by refluxing 4.7 g. (0.02 moles) of 4-trifluoromethylphthalic acid in 50 ml. of acetic anhyride containing 1 drop of concentrated sulfuric acid for 4 hours. Evaporation to dryness under reduced pressure affords the crude anhydride as a dark solid. To the crude anhydride is added 8.2 g. (0.040 moles) of 3-trifluoromethylphenylacetic acid and 400 mg. of anhydrous sodium acetate. The mixture is heated at 275° C. for 2 hours, under nitrogen, and the residue subjected to high vacuum for approximately 15 minutes. The residue is then combined with 25 ml. of methanol and a solution of 8.7 g. (0.16 moles) of sodium methoxide and 100 ml. of methanol. After refluxing for three-fourths of an hour, and evaporation to dryness, the residue is dissolved in 300 ml. of water and extracted three times with 200 ml. portions of ether. Owing to the influence of the two lypophilic trifluoromethyl substituents, the sodium salt of the 1,3-indandione is extracted into the ether. Evaporation of the ether extracts affords the crude sodium salt, which is then dissolved in water and the resultant solution acidified. The red 2-(3'-trifluoromethylphenyl)-5-trifluoromethyl-1,3-indandione which separates from solution is filtered. Yield: 7.1 g. (50 percent); m.p. 129°–131° C.

Anal. Calc'd for $C_{17}H_8F_6O_2$: C, 56.99; H, 2.25.
Found: C, 57,12; H, 2.59.

EXAMPLE XI

A thorough mixture of 0.020 moles of 4-trifluoromethylphthalic anhydride, 0.020 moles of 2-naphthylacetic acid, and 200 mg. of anhydrous sodium acetate, is heated under nitrogen at 270° C. for about 3 hours. After cooling, the residue is subjected to high vacuum for approximately 15 minutes and dissolved in 50 ml. of methanol. To this solution is then added 4.3 g. (0.080 moles) of sodium methoxide in 30 ml. of methanol. The resulting dark red solution is refluxed 1 hour, cooled, and evaporated to dryness. The residue is dissolved in 150 ml. of water, and the resultant solution is acidified with 6N HCl to afford crude 2-(2'-naphthyl)-5-trifluoromethyl-1,3-indandione. Yield: 27 percent; m.p. 189.5°–191° C. (ethanol).

Anal. Calc'd for $C_{20}H_{11}F_3O_2$: C, 70.58; H, 3.26.
Found: C, 70.64; H, 3.60.

Using the above procedure, the compounds in table V are prepared from the appropriate starting materials.

TABLE V

2-aryl-1,3-indandione	Crystallization solvent	Yield, percent	M.P., ° C.
2-(3'-methylphenyl)-5-trifluoromethyl-1,3-indandione	Ethanol-water.	38	126–128
2-(3'-methoxyphenyl)-5-trifluoromethyl-1,3-indandione	Isopropanol-water.	33	166.5–168
2-(3'-bromophenyl)-5-trifluoromethyl-1,3-indandione	Ethanol-water.	19	172.5–174

Similarly, the following compounds are also prepared:
2-(4'-trifluoromethylsulfonylphenyl)-5-trifluoromethyl-1,3-indandione
2-(3'-trifluoromethylsulfonylphenyl)-5-trifluoromethyl-1,3-indandione
2-(4'-methylphenyl)-5-trifluoromethyl-1,3-indandione
2-(2'-methoxyphenyl)-5-trifluoromethyl-1,3-indandione
2-(4'-bromomethyl)-5-trifluoromethyl-1,3-indandione

EXAMPLE XII

2-(3'-Trifluoromethylphenyl)-4-trifluoromethyl-1,3-indandione is prepared from 3-trifluoromethylphthalic anhydride and 3-trifluoromethylphenylacetic acid according to the procedure of example X.

EXAMPLE XIII

The following compounds are prepared from 3-trifluoromethylphthalic anhydride and the appropriately substituted arylacetic acids according to the method of example XI:
2-(2'-naphthyl)-4-trifluoromethyl-1,3-indandione
2-(3'-methylphenyl)-4-trifluoromethyl-1,3-indandione
2-(3'-methoxyphenyl)-4-trifluoromethyl-1,3-indandione
2-(3'-bromophenyl)-4-trifluoromethyl-1,3-indandione
2-(4'-trifluoromethylsulfonylphenyl)-4-trifluoromethyl-1,3-indandione 2-(3'-trifluoromethylsulfonylphenyl)-4-trifluoromethyl-1,3-indandione
2-(4'-methylphenyl)-4-trifluoromethyl-1,3-indandione
2-(2'-methoxyphenyl)-4-trifluoromethyl-1,3-indandione
2-(4'-bromomethyl)-4-trifluoromethyl-1,3-indandione

EXAMPLE XIV

A thorough mixture of 0.030 moles of 4-methylphthalic anhydride, 0.030 moles of 3-methoxyphenylacetic acid, and 100 mg. of anhydrous sodium acetate is heated under nitrogen at 290° C. for 3 hours. The resultant product is triturated with 75 ml. of 10 percent sodium bicarbonate and filtered, and the filtered material is dried under vacuum over phosphorous pentoxide. Combination of the resulting dry solid with 15 ml. of methanol and 2.2 g. (0.045 moles) of sodium methoxide in 50 ml. of methanol produces a red solution which is refluxed for one-half hour and evaporated to dryness. The residue is dissolved in water and the resultant solution acidified with excess 6N hydrochloric acid. The crude red 2-(3'-methoxyphenyl)-5-methyl-1,3-indandione which separates from solution is filtered and recrystallized from ethanol. Yield 53 percent; m.p. 100°–102° C.

Anal. Calc'd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30.
Found: C, 76.62; H, 5.36.

Using the above procedure, the compounds in table VI are prepared from the appropriate starting materials.

TABLE VI

2-aryl-1,3-indandione	Crystallization solvent	Yield, percent	M.P., ° C.
2-(2'-bromophenyl)-5-methyl-1,3-indandione.	Ethanol	40	131–133
2-(3'-chlorophenyl)-5-methyl-1,3-indandione.	do	72	123–125

The compounds below are also prepared according to the above procedure from the appropriately substituted starting materials:
2-(3'-trifluoromethylsulfonyl)-5-methyl-1,3-indandione
2-(2'-naphthyl)-5-methyl-1,3-indandione
2-(4'-bromophenyl)-5-methyl-1,3-indandione
2-(4'-chlorophenyl)-5-methyl-1,3-indandione
2-(2'-methoxyphenyl)-5-methyl-1,3-indandione

2-(3'-methoxyphenyl)-4-methyl-1,3-indandione
2-(3'-trifluoromethylsulfonyl)-4-methyl-1,3-indandione
2-(2'-naphthyl)-4-methyl-1,3indandione
2-(4'-bromophenyl)-4-methyl-1,3-indandione
2-(4'-chlorophenyl)-4-methyl-1,3-indandione
2-(2'-methoxyphenyl)-4-methyl-1,3-indandione

EXAMPLE XV

2,3-naphthalene dicarboxylic acid anhydride is prepared by refluxing 4.3 g. (0.02 moles of 2,3-naphthalenedicarboxylic acid in 50 ml. of acetic hydride containing 2 drops of concentrated sulfuric acid for 2 hours. The mixture is evaporated to dryness and the resulting anhydride is thoroughly mixed with 3.0 g. (0.02 moles) of m-tolyacetic acid and 100 mg. of sodium acetate. The mixture is heated under nitrogen at 270° C. for 3 hours and cooled. To the resultant solid is added 20 ml. of methanol and a solution of 3.3 g. (0.06 moles) of sodium methoxide in 50 ml. of methanol. After refluxing 1 hour and evaporating to dryness, the residue is dissolved in 250 ml. of water and the solution extracted with ether. The aqueous phase is acidified with 6N hydrochloric acid, and the orange solid which separates from solution is recrystallized from 1 liter of boiling acetone to give in several crops 2.2 g. (39 percent) of 2-(3'-methylphenyl)-2,3-dihydrobenz[f]indene-1,3-dione. M.p. 258°–260° C.

Anal. Calc'd for $C_{20}H_{14}O_2$:		C, 83.39;	H, 4.94.
	Found:	C, 83.72;	H, 4.95.

Using the above procedure, the compounds in Table VII are prepared from the appropriate starting materials:

TABLE VII

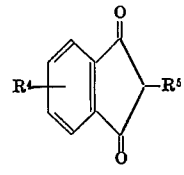
2-aryl-2,3-dihydrobenz[f]indene-1,3-dione	Crystallization solvent	Yield, percent	M.P., ° C.
2-(3'trifluoromethylphenyl)-2,3-dihydrobenz[f]indene-1,3-dione.	Ethanol	75	262-264
2-(2'-naphthyl)-2,3-dihydrobenz[f]indene-1,3-dione.	do	14	[1] 293-294

[1] Decomposition.

The compounds below are also prepared according to the above procedure from the appropriate starting materials:
2-(3'-bromophenyl)-2,3-dihydrobenz[f]indene-1,3-dione
2-(4'-iodophenyl)-2,3-dihydrobenz[f]indene-1,3-dione
2-(2'-methoxyphenyl)-2,3-dihydrobenz[f]indene-1,3-dione
2-(3'-trifluoromethylsulfonylphenyl)-2,3-dihydrobenz[f]indene-1,3-dione

What is claimed is:

1. A compound selected from the group consisting of those having the formula:



where R^4 is selected from the group consisting of —Br, and —CF_3; and R^5 is selected from the group consisting of methoxyphenyl, bromophenyl, trifluoromethylphenyl, trifluoromethylsulfonylphenyl, and 2-naphthyl.

2. 2-(2'-naphthyl)-5-bromo-1,3-indandione.

3. 2-(3'-methylphenyl)-5-trifluoromethyl-1,3-indandione.

4. 2-(2'-naphthyl)-5-trifluoromethyl-1,3-indandione.

* * * * *