

PATENT SPECIFICATION

(11) 1 474 459

1 474 459

- (21) Application No. 43372/74 (22) Filed 7 Oct. 1974
 (31) Convention Application No. 405 736
 (32) Filed 11 Oct. 1973
 (31) Convention Application No. 492 651
 (32) Filed 30 July 1974 in
 (33) United States of America (US)
 (44) Complete Specification published 25 May 1977
 (51) INT CL³ C07C 59/25; A61K 31/38, 31/41, 31/165, 31/185, 31/215;
 C07C 69/67, 101/00, 103/00, 121/64, 143/00, 147/00,
 149/40; C07D 257/04, 333/04, 409/12 (C07D 409/12,
 257/04, 333/22)



(52) Index at acceptance

C2C 1175 1204 1228 1464 1510 200 204 215 220 221 225 226
 227 22X 22Y 246 250 252 254 25Y 282 292 29X 29Y
 302 304 305 30Y 311 313 314 316 318 31Y 321 326
 32Y 332 337 338 339 342 34Y 351 353 355 35X 35Y
 364 365 366 367 368 36Y 376 385 388 389 39Y 421
 42Y 43X 440 47X 490 491 500 509 50Y 510 51X 532
 583 591 60X 618 620 621 623 624 625 628 62X 62Y
 638 650 656 658 65X 660 661 662 665 666 681 697
 699 776 778 790 79Y KM KR LZ MB MK NN QE
 SF UB UN UQ UR

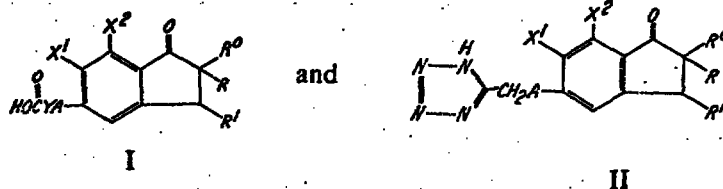
A5B 29X 29Y 332 334 33Y 382 384 38Y 392 394 39X 420
 421 423 42Y 430 431 433 43Y 442 443 444 44Y 451
 45Y 47X 47Y 480 482 483 484 485 486 48Y 491 492
 493 49Y 500 502 50Y 542 543 54Y 565 56Y 586 58Y
 595 596 597 59Y 605 606 60Y 640 641 647 64Y 650
 654 65X 65Y 77Y

- (72) Inventors EDWARD J. CRAGOE JR. and OTTO WILLIAM
 WOLTERS DORF JR.

(54) SUBSTITUTED INDANONES

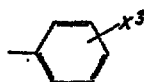
(71) We, MERCK & CO. INC., a corporation duly organised and exist-
 ing under the laws of the State of New Jersey, United States of America, of
 Rahway, New Jersey 07065, United States of America, do hereby declare the
 invention, for which we pray that a patent may be granted to us and the method by
 which it is to be performed, to be particularly described in and by the following
 statement:—

This invention provides 2-aryl or thienyl substituted indanones having the
 following formulae:



10

in which R⁰ is



or



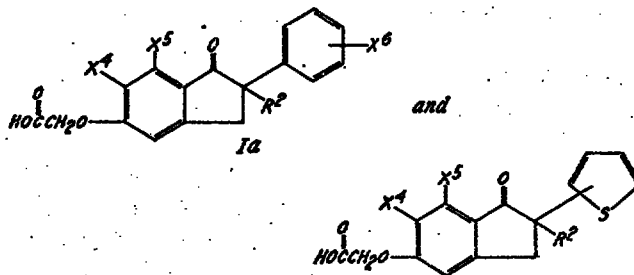
10

where Y is alkylene or haloalkylene containing from 1 to 4 carbon atoms, X³ is

hydrogen, halogen, viz. chlorine, bromine, fluorine or iodine, C_{1-3} alkyl, e.g. methyl, ethyl, *n*-propyl, *n*-butyl; tertiary butyl or *n*-pentyl, cycloalkyl, e.g. cyclopentyl or cyclohexyl, C_{1-3} alkoxy, e.g. methoxy, nitro, hydroxy, amino, cyano, sulfamoyl, methanesulfonyl, aminomethyl, chlorosulfonyl, acylamino or acylaminomethyl; X^1 is hydrogen, aminomethyl, C_{1-3} alkyl such as methyl or halogen, viz. chlorine, bromine, fluorine or iodine; X^8 is hydrogen or C_{1-3} alkyl such as methyl; A is oxygen or sulfur; R is C_{1-3} alkyl, e.g. methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl or pentyl, cycloalkyl, preferably C_{3-6} cycloalkyl, e.g. cyclopentyl or cyclohexyl, cycloalkyl- $(C_{1-3}$ alkyl), e.g. cyclopropylmethyl or cyclopentylmethyl, C_{1-3} alkenyl, e.g. allyl, (1,2 or 3)-butenyl or (1,2,3 or 4)-pentenyl, phenyl- $(C_{1-3}$ alkyl), e.g. benzyl, phenethyl or phenylpropyl, phenyl- $(C_{1-3}$ alkenyl) e.g. cinnamyl, aryl, e.g. phenyl or thienyl, or substituted aryl, e.g. haloaryl, $(C_{1-3}$ alkyl)-aryl, or $(C_{1-3}$ alkoxy)-aryl; and R^1 is hydrogen, C_{1-3} alkyl or aryl, e.g. phenyl; or R and R^1 are joined to form a C_{1-4} bivalent hydrocarbon chain; and X^1 is hydrogen, methyl or halo, e.g. chlorine, bromine or fluorine and X^2 is methyl, trihalomethyl or halo, e.g. chlorine, bromine or fluorine or X^1 and X^2 are joined to form a bivalent hydrocarbon chain containing 3 or 4 carbon atoms, for example, trimethylene, tetramethylene or 1,3-butadienylene; and the non-toxic pharmacologically acceptable salts, amides, anhydrides and esters thereof.

The preferred compounds of this invention are those compounds in which A is oxygen and R, R^0 , R^1 , R^2 , X^1 , X^2 , X^3 , X^7 and X^8 are as defined above.

Particularly preferred compounds of this invention are 1-oxo-2-aryl-2-substituted-6,7-disubstituted-5-indanyloxyacetic acids having the following formulae:



where R^2 and C_{1-3} alkyl, viz. methyl, ethyl, *n*-propyl or isopropyl, or C_{3-6} cycloalkyl, e.g. cyclopropyl, cyclopentyl or cyclohexyl; each of X^4 and X^5 , which are the same or different, is methyl or chlorine; and X^6 is hydrogen, methyl, chlorine or fluorine, and their non-toxic pharmaceutically acceptable salts.

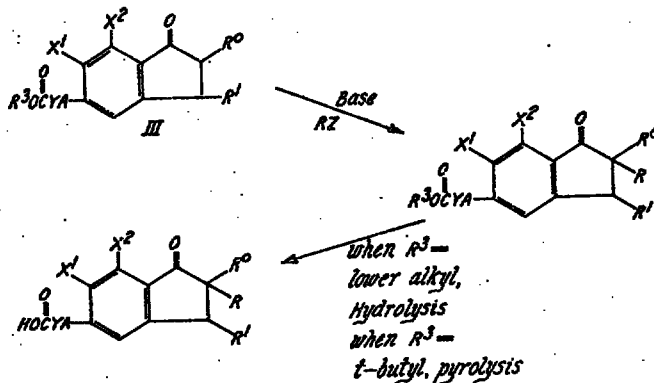
Pharmacological studies have shown that the compounds falling within the above definition are effective diuretic and saluretic agents and so can be used in the treatment of conditions associated with electrolyte and fluid retention. Such compounds are also useful in the treatment of hypertension, and are able to maintain the uric acid concentration in the body at pretreatment levels or to even effect a decrease in the uric acid concentration when administered in therapeutic dosages in conventional vehicles.

Many currently available diuretics and saluretics have a tendency upon administration to induce hyperuricemia. This may precipitate uric acid and/or sodium urate in the body, which may cause from mild to severe cases of gout. This invention now provides effective compounds to treat those patients requiring diuretic and saluretic treatment without incurring the risk of inducing gout. In fact, when used in appropriate doses, compounds of this invention can function as uricosuric agents.

Compounds in the foregoing class have been found to exhibit particularly good diuretic/saluretic activity. Such compounds also either maintain the uric acid concentration of the body at pretreatment levels or even cause a decrease in uric acid concentration.

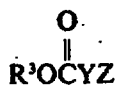
Several methods may be used to prepare the substituted indanones of this invention. One method comprises 2-alkylation of a [1-oxo-2-aryl or 2-thienyl-5-indanyl(oxy or thio)]alkanoic acid or ester of structure III (infra) with an alkylating agent of the formula RZ where Z is halo. This reaction is conducted by first treating the [1-oxo-2-aryl or 2-thienyl-5-indanyl(oxy or thio)]alkanoic acid or ester with a suitable base, for example an alkali metal hydride such as sodium hydride, an alkali metal alkoxide such as potassium tertiary butoxide or sodium methoxide, or an alkali metal amide such as sodium amide or lithium amide. The resulting

carbanion is then treated with the alkylating agent, RZ. Any solvent that is inert or substantially inert to the reactants may be used. Suitable solvents include for example, 1,2-dimethoxyethane, tertiary butanol, benzene and dimethylformamide. The reaction may be conducted at a temperature in the range of from 0°C to 150°C. In general, the reaction is conducted at a temperature in the range of from 0–50°C. The following equation illustrates this process:

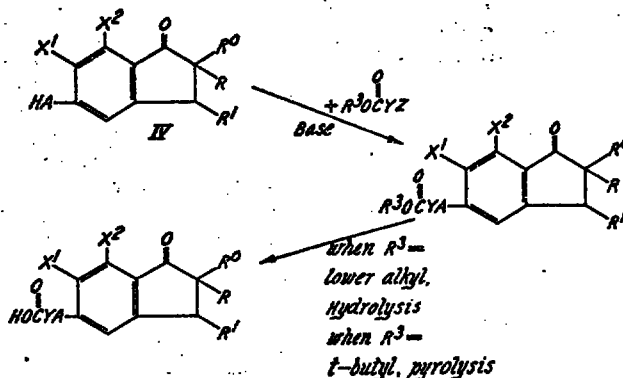


where A, R, R⁰, R¹, X¹, X², X³, X⁴, Z and Y are as defined above and R³ is hydrogen or C_{1–3} alkyl.

A second method for preparing the [1-oxo-2-aryl-2-substituted-5-indanyl-oxy(or thio)]alkanoic acids of this invention comprises reacting a halo alkanoic acid or ester thereof,



with a suitable 2-aryl or 2-thienyl-2-substituted-5-hydroxy(or mercapto)-1-indanone (IV):

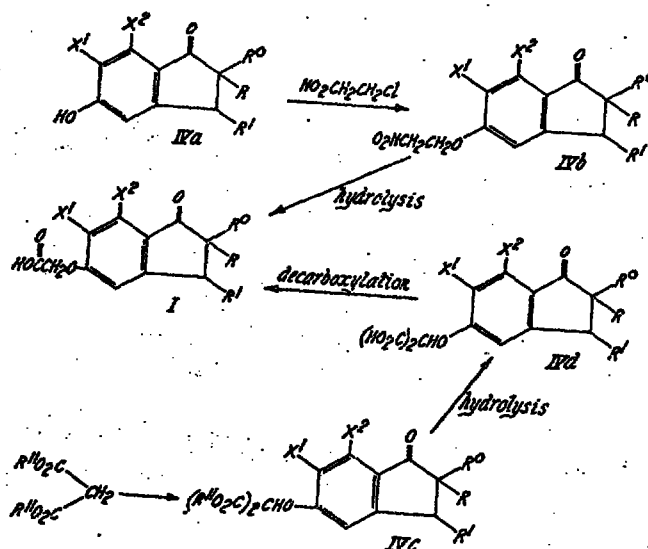


where all substituents are as defined above.

In general, the reaction is conducted in the presence of a base such as an alkali metal carbonate, hydroxide or alkoxide such as potassium carbonate, sodium carbonate, potassium hydroxide, sodium hydroxide or sodium methoxide. Any solvent that is inert or substantially inert to the reactants and in which the reagents are reasonably soluble may be used. Acetone, ethanol and dimethylformamide for example have proven to be particularly advantageous solvents. The reaction may be conducted at a temperature in the range of from 25°C. to the reflux temperature of the solvent. If the haloalkanoic acid ester is used, the ester obtained may be hydrolysed to the free acid by well known methods. When R³ is the *tert*-butyl group, the acid may be obtained by acid-catalysed pyrolysis, such as by heating the *tert*-butyl ester in the presence of a strong acid, for example, in the presence of *p*-toluene-sulfonic acid, sulfuric acid or gaseous hydrogen chloride. In general, pyrolysis is effected by heating at a temperature in the range from 70° to

140°C., preferably 80°—100°C. Also, the pyrolysis may be conducted without a solvent or in the presence of a suitable non-aqueous medium in which the reactants are reasonably soluble, for example, in the presence of benzene, toluene or xylene.

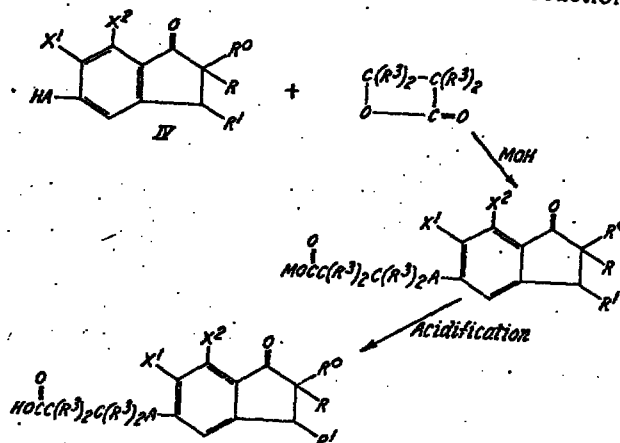
Two additional processes for preparing compounds of Formula I are as illustrated by the following flow diagram:



The first process shown involves reacting a 5-hydroxy (or mercapto) compound (IVa supra) with halonitro ethane to form a 2-nitroethane, (Formula IVb) which upon hydrolysis yields the end product (I). The preparation of the compound of Formula IVb is shown in British Patent No. 1,325,528.

In the other process shown, the 5-hydroxy (or mercapto) compound (IVa) is reacted with a malonic ester (where R'' is C_1 -alkyl, preferably ethyl) to form a compound (IVc); this is hydrolysed to form another intermediate compound (Formula IVd) which is then decarboxylated to form the end product I.

Those 2-aryl or 2-thienyl substituted indanones of this invention in which the alkylene chain, Y, contains two linear carbon atoms between the carboxy and oxy or thio groups are prepared from the corresponding 5-(hydroxy or mercapto) compounds (IV) by the reaction of the latter with propiolactone or with an appropriately substituted propiolactone in the presence of a base such as an aqueous solution of sodium hydroxide, preferably while heating the solution at reflux temperatures followed by the acidification of the carboxylate thus formed to the desired acid. The following equation illustrates the reaction:



where all substituents are as defined above and M is an alkali metal cation, which may be derived from an alkali metal hydroxide or alkali metal carbonate, such as sodium or potassium cation.

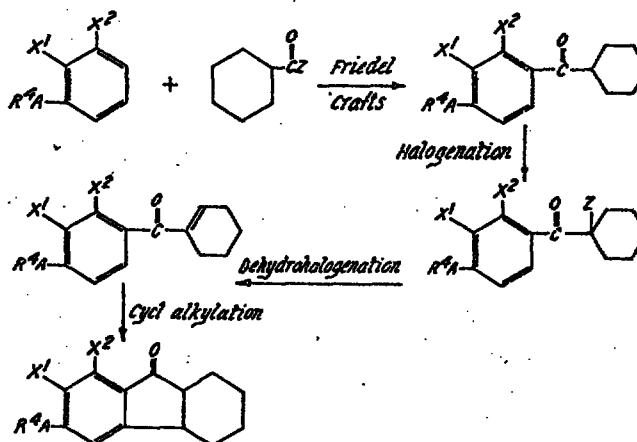
The 2-aryl or 2-thienyl-2-substituted-5-hydroxy(or mercapto)-1-indanones (IV, supra) are novel compounds. They are claimed in, and their preparation is described and claimed in, the specification of our copending application No. 26849/76, Serial No. 1,474,460.

Those compounds of the invention in which R and R' are joined to form a cyclopropyl ring (XIII, infra) are prepared by treating a (1-oxo-2-indene-5-yloxy)-alkanoic acid (XII) with an alkali metal base such as sodium hydride followed by treatment with a methylating agent, for example trimethylsulfoxonium iodide. The (1-oxo-2-indene-5-yloxy)alkanoic acids described in U.S. Patent 3,668,241. The following equation illustrates this process:



where all substituents are as defined above.

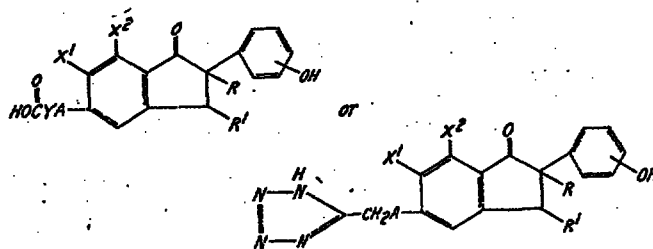
The nuclear C₁₋₃ alkoxy precursors of those compounds of the invention in which R and R' are joined to form a cyclohexyl ring are prepared according to the procedure described and claimed in the specification of our co-pending application No. 46938/73, Serial No. 1,427,090:



where the substituents are as defined above.

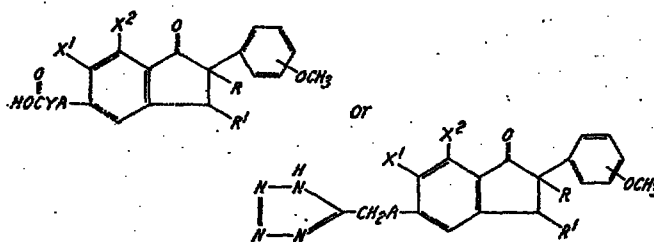
Those compounds of formula I in which R⁰ is aryl and the X³ substituents are cyano, chlorosulfonyl, sulfamoyl, nitro, amino or aminomethyl are generally prepared from the compounds of formula I or an intermediate compound such as a compound of formula IV where R⁰ is unsubstituted aryl or thienyl or from a compound of formula IV or I where R⁰ is substituted aryl when the substituents can be converted to the desired substituent by well known methods. For example, when R⁰ is unsubstituted aryl the compounds of formula I can be reacted with chlorosulfonic acid to yield a compound in which X³ is chlorosulfonyl and the latter compound reacted with ammonia to yield a compound of formula I in which X³ is sulfamoyl.

Compounds of the formula:

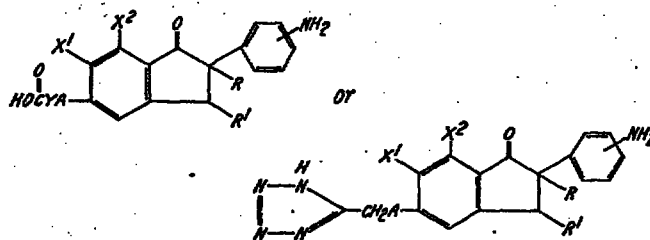


in which A, R, R', Y, X¹ and X² are as defined above, are conveniently prepared in

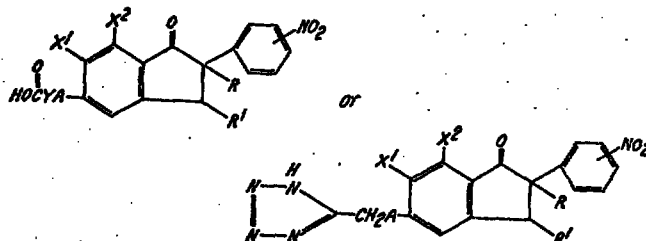
accordance with the present invention by treating a compound of the formula:



with an ether-cleaving reagent, e.g. hydrogen bromide in acetic acid.
Compounds of the formula:



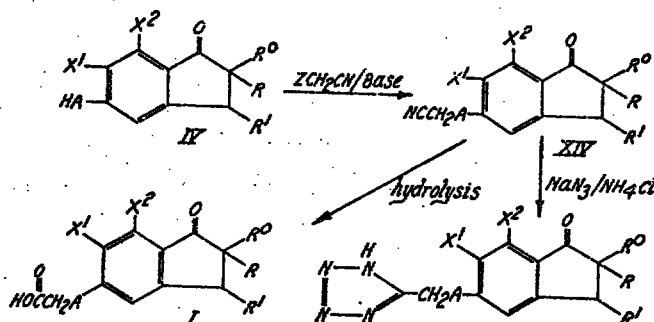
in which A, R, R¹, Y, X¹ and X² are as defined above, are conveniently prepared by reducing a compound of the formula:



Other conversions are shown in the examples (see for instance Examples 21, 22 and 31).

Also included within the scope of this invention are the esters and amides of the acids which are prepared by known methods. Thus, for example, the esters may be prepared by the reaction of the [1-oxo-2-aryl or 2-thienyl-2-substituted-5-indanyloxy(or thio)]-alkanoic acid of this invention with an alcohol, for example, with a C₁₋₃ alkanol. The amides may be prepared by converting a [1-oxo-2-aryl or 2-thienyl-2-substituted-5-indanyloxy(or thio)]-alkanoic acid to its corresponding acid chloride by treatment with thionyl chloride followed by treating said acid chloride with ammonia, an appropriate mono-(C₁₋₃ alkyl)amine, di-(C₁₋₃ alkyl)amine or a hetero amine, such as piperidine or morpholine, to produce the corresponding amide. To the extent that the esters and amides are both non-toxic and pharmacologically acceptable they are the functional equivalent of the corresponding free acids.

In addition to the salts, esters and amides being functionally equivalent to the carboxylic products, those compounds in which the carboxyl group is replaced by a 5-tetrazolyl radical are also functionally equivalent to the carboxylic acids. These tetrazole analogues are prepared as depicted in the following equation:



(Formula I where Y is methylene)
where all substituents are as defined above.

The 5-hydroxy (or thio)-1-indanone (IV above) is treated with a haloacetonitrile such as chloroacetonitrile, bromoacetonitrile or iodoacetonitrile in the presence of a base such as potassium carbonate in a suitable solvent such as acetone, dimethylformamide or dimethoxyethane at a temperature in the range of from 25° to 100°C. to afford the corresponding nitrile (XIV) which upon treatment with sodium azide and ammonium chloride in dimethylformamide at a temperature in the range of from 25° to 100°C, affords the 5-[1-oxo-2-aryl or 2-thienyl-2-substituted-5-indanyloxy (or thio)methyl]tetrazole.

A still further process for preparing compounds of Formula I (the end product) in which Y is methylene involves hydrolysis of the nitrile compound shown in Formula XIV above. This is a typical and well known hydrolysis.

Many of the compounds of the invention contain an asymmetric carbon atom in the 2-position of the indanyl ring. When this situation exists, the optical antipodes may be separated by methods described below. This invention embraces, therefore, not only the racemic [1-oxo-2-aryl or 2-thienyl-2-substituted-5-indanyloxy(or thio)]alkanoic acids but also their optically active antipodes.

Separation of the optical isomers of the racemic acids may be accomplished by forming a salt of the racemic mixture with an optically active base such as (+) or (-) amphetamine, (-)-cinchonidine, dehydroabietylamine, (+ or -)-α-methylbenzylamine, (+) or (-)-α-(1-naphthyl)ethylamine, brucine or strychnine in a suitable solvent such as methanol, ethanol, 2-propanol, benzene, acetonitrile, nitromethane or acetone. There is thus formed in the solution two diastereoisomeric salts one of which is usually more soluble in the solvent than the other. Repetitive recrystallization of the crystalline salt generally affords a pure diastereoisomer. The optically pure 2-aryl or 2-thienyl indane acid is obtained by acidification of the salt with a mineral acid, extraction into ether, evaporation of the solvent and recrystallization of the optically pure antipode.

The other optically pure antipode may generally be obtained by using a different base to form the diastereoisomeric salt. It is of advantage to isolate the partially resolved acid from the filtrates of the purification of the one diastereoisomeric salt and to further purify this substance through the use of another optically active base.

The examples which follow illustrate some of the 2-aryl and 2-thienyl indane products of the invention and the methods by which they are prepared. In the examples, proportions of recrystallization solvents are on a volume basis, and the screen and capsule sizes are U.S. standards.

EXAMPLE 1.

Preparation of (1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid

Step A: 2,3-Dichloro-4-phenylacetylanisole

To a stirred mixture of 2,3-dichloroanisole (62 g., 0.35 mole), phenylacetyl chloride (54 g., 0.35 mole) and carbon disulfide (250 ml.) is added portionwise aluminium chloride (47 g., 0.35 mole) with cooling at 0-5°C. The reaction mixture is left at 25°C for 17 hours, the carbon disulfide removed, and the residue treated with ice-water and concentrated hydrochloric acid (50 ml.) to give 68.8 g. of 2,3-dichloro-4-phenylacetylanisole, which melts at 126-129°C. on crystallization from benzene:cyclohexane, 2:1.

Elemental analysis for $C_{13}H_{12}Cl_2O_2$:

Calc.: C, 61.04; H, 4.10;

Found: C, 61.46; H, 4.11.

Step B: 2,3-Dichloro-4-(2-phenylacryloyl)anisole

Acetic anhydride (100 ml.) is added dropwise to a suspension of 2,3-dichloro-4-phenylacetylanisole (29.5 g., 0.01 mole) in bis(dimethylamino)methane (100 ml.) under nitrogen with cooling to maintain the reaction mixture at a temperature below 60°C. The reaction mixture is stirred at 25°C. for 2 hours, and poured into ice water (1500 ml.) to precipitate 7.4 g. of 2,3-dichloro-4-(2-phenylacryloyl)-anisole which melts at 87–89°C.

Elemental analysis for $C_{16}H_{12}Cl_2O_2$:

Calc.: C, 62.56; H, 3.94;

Found: C, 62.67; H, 4.04.

Step C: 2-Phenyl-5-methoxy-6,7-dichloro-1-indanone

2,3-Dichloro-4-(2-phenylacryloyl)anisole (7.4 g., 0.024 mole) is added portionwise to cold, concentrated sulfuric acid (150 ml.) with stirring. The reaction mixture is stirred in an ice bath for 2 hours, then added dropwise to ice-water to precipitate 3.91 g of 2-phenyl-5-methoxy-6,7-dichloro-1-indanone, which melts at 193–195°C. upon crystallization from benzene:cyclohexane, 1:2.

Elemental analysis for $C_{16}H_{12}Cl_2O_2$:

Calc.: C, 62.56; H, 3.94;

Found: C, 62.84; H, 4.00.

Step D: 2-Phenyl-5-hydroxy-6,7-dichloro-1-indanone

A stirred mixture of 2-phenyl-5-methoxy-6,7-dichloro-1-indanone (3.91 g., 0.0127 mole) and pyridine hydrochloride (40 g.) is heated at 190°C. for one hour, then poured into water (600 ml.). The 2-phenyl-5-hydroxy-6,7-dichloro-1-indanone, which separates (2.48 g.), melts at 250–252°C. after recrystallization from ethanol:water, 2:1.

Elemental analysis for $C_{15}H_{10}Cl_2O_2$:

Calc.: C, 61.46; H, 3.44;

Found: C, 60.94; H, 3.66.

Step E: (1-Oxo-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid

2-Phenyl-5-hydroxy-6,7-dichloro-1-indanone (5.86 g., 0.023 mole), iodoacetic acid (4.28 g., 0.023 mole), potassium carbonate (3.04 g., 0.022 mole) and acetone (250 ml.) are heated at reflux for 48 hours. The reaction mixture is cooled to 25°C. and concentrated *in vacuo* to give a solid product which is dissolved in water and acidified with 6*N* hydrochloric acid to precipitate 6.8 g. of a mixture of (1-oxo-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid and 2-phenyl-5-hydroxy-6,7-dichloro-1-indanone. The phenol is removed by crystallization with nitromethane. Concentrating the filtrate to dryness *in vacuo* and triturating with toluene gives 470 mg. of (1-oxo-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid which melts at 181–185°C.

Elemental analysis for $C_{17}H_{12}Cl_2O_4$:

Calc.: C, 58.14; H, 3.45; Cl, 20.19;

Found: C, 58.17; H, 3.54; Cl, 19.94.

Step F: (1-oxo-2-phenyl-2-methyl-6,7-dichloro-5-indanyloxy)acetic acid

A stirred solution of (1-oxo-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid (0.351 gm., 0.001 mole) in dimethylformamide (7 ml.) is cooled in an ice bath, treated with sodium hydride (0.084 g. of a 57% oil dispersion, 0.002 mole) and stirred for two hours. Methyl iodide (1 ml.) is added and the reaction mixture is stirred at 25°C. for two hours, poured into ice water, and acidified with dilute aqueous hydrochloric acid affording (1-oxo-2-phenyl-2-methyl-6,7-dichloro-5-indanyloxy)acetic acid, which melts at 168–169°C.

EXAMPLE 2.

Where in Example 1, Step A, there is substituted for the 2,3-dichloroanisole an equivalent amount of 2-chloro-3-methylanisole, 2,3-dimethylanisole, 3-methyl-

(20)

8
5
chloro-
0 ml.)
rature
d into
loyl)-
10
tion-
ction
er to
its at
15
20
1 g.,
cur,
o-l-
tion.
30
etic
one
°C.
and
-2-
5,7-
ne.
470
at
35
40
45
did
th,
nd
is
te
5-
50
le
l-
55

9	1,474,459	9
	aniso, or 2-methyl-3-chloroaniso, respectively, and Steps B to F are carried out as described, there is obtained:	
	(1-oxo-2-phenyl-2,7-dimethyl-6-chloro-5-indanyloxy)acetic acid,	
	(1-oxo-2-phenyl-2,6,7-trimethyl-5-indanyloxy)acetic acid,	
5	(1-oxo-2-phenyl-2,7-dimethyl-5-indanyloxy)acetic acid, or	5
	(1-oxo-2-phenyl-2,6-dimethyl-7-chloro-5-indanyloxy)acetic acid.	
	EXAMPLE 3.	
10	Where in Example 1, there is substituted for the phenylacetyl chloride of Step A an equivalent amount of <i>p</i> -methylphenylacetyl chloride, <i>m</i> -methylphenylacetyl chloride, <i>o</i> -chlorophenylacetyl chloride or <i>p</i> -fluorophenylacetyl chloride, and Steps B to F are carried out as described, there is obtained respectively:	10
	[1-oxo-2-methyl-2-(4-methylphenyl)-6,7-dichloro-5-indanyloxy]acetic acid,	
	[1-oxo-2-methyl-2-(3-methylphenyl)-6,7-dichloro-5-indanyloxy]acetic acid,	
	[1-oxo-2-(2-chlorophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid, or	
15	[1-oxo-2-(4-fluorophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid.	15
	EXAMPLE 4.	
	Where in Example 1, the 2-alkylating agent, methyl iodide, of Step F is replaced by an equivalent amount of ethyl iodide, allyl bromide, benzyl bromide, or cinnamyl bromide, respectively, there is obtained, respectively:	
20	(1-oxo-2-ethyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid,	20
	(1-oxo-2-allyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid,	
	(1-oxo-2-benzyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid, or	
30	(1-oxo-2-cinnamyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid.	
	EXAMPLE 5.	
25	(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid	25
	Step A: 2',3'-Dichloro-4'-methoxyisobutyrophenone	
30	A stirred mixture of 2,3-dichloroaniso (I) (100 g., 0.565 mole) and isobutyryl chloride (II) (66 g., 0.62 mole) in methylene chloride (400 ml.) is cooled to 5°C. and treated with aluminium chloride (83 g., 0.62 mole) during a one-hour period. The reaction mixture is allowed to warm to 25°C. and after 24 hours is poured into ice water (400 ml.) and hydrochloric acid (30 ml.). The organic phase is washed with 5% sodium hydroxide and water, dried over magnesium sulfate and distilled at reduced pressure affording 68 g. of 2',3'-dichloro-4'-methoxyisobutyrophenone (III), which distils at 120°—130°C/0.5 mm.	30
35	Elemental analysis for C ₁₁ H ₁₂ Cl ₂ O ₂ :	35
	Calc.: C, 53.46; H, 4.89;	
40	Found: C, 54.25; H, 5.07.	
	Step B: 2-Bromo-2',3'-dichloro-4'-methoxyisobutyrophenone	
45	A stirred solution of 2',3'-dichloro-4'-methoxyisobutyrophenone (45 g., 0.183 mole) in acetic acid (150 ml.) is treated during one-half hour with bromine (30 g., 0.187 mole). The reaction mixture is stirred for 10 minutes, then poured into ice water (600 ml.) containing sodium bisulfite (2 g.). The 2-bromo-2',3'-dichloro-4'-methoxyisobutyrophenone (IV), which separates (48 g.), melts at 72°—73°C. after recrystallization from hexane.	45
	Elemental analysis for C ₁₁ H ₁₁ BrCl ₂ O ₂ :	
50	Calc.: C, 40.52; H, 3.40;	
55	Found: C, 40.68; H, 3.38.	

Step C: 2-Methylene-2',3'-dichloro-4'-methoxypropiophenone

A solution of 2-bromo-2',3'-dichloro-4'-methoxyisobutyrophenone (32 g., 0.1 mole) and anhydrous lithium bromide (17.4 g., 0.2 mole) in DMF (200 ml.) is stirred at 95°C. in an inert atmosphere for three hours and poured into ice water (500 ml.). The 2-methylene-2',3'-dichloro-4'-methoxypropiophenone (V), which separates, melts at 59°C. after recrystallization from petroleum ether.

Elemental analysis for $C_{11}H_{10}Cl_2O_2$:

Calc.: C, 53.90; H, 4.11;

Found: C, 53.72; H, 4.11.

Step D: 2-Methyl-5-methoxy-6,7-dichloro-1-indanone

A solution of 2-methylene-2',3'-dichloro-4'-methoxypropiophenone (40 g., 0.163 mole) in concentrated sulfuric acid (75 ml.) is allowed to stand at 25°C. for 24 hours and is then slowly poured into vigorously stirred ice water (500 ml.). The 2-methyl-5-methoxy-6,7-dichloro-1-indanone, which separates (40 g.), melts at 129°C. after recrystallization from methylcyclohexane.

Elemental analysis for $C_{11}H_{10}Cl_2O_2$:

Calc.: C, 53.90; H, 4.11;

Found: C, 53.84; H, 4.00.

Step E: 2-Methyl-2-phenyl-5-methoxy-6,7-dichloro-1-indanone

Potassium *tert*-butoxide (8.42 g., 0.075 mole) dissolved in *tert*-butanol (300 ml.) is added to a refluxing solution of 2-methyl-5-methoxy-6,7-dichloro-1-indanone (12.26 g., 0.05 mole). Refluxing is continued for 2 hrs., then a suspension of diphenyliodonium chloride (19.0 g., 0.06 mole) in *tert*-butanol (1 l.) is added and refluxing is continued for a further 2 hrs. The reaction mixture is cooled to 25°C., 300 ml. of water added, and the mixture concentrated to dryness *in vacuo* to give 4.97 g. of 2-methyl-2-phenyl-5-methoxy-6,7-dichloro-1-indanone, which melts at 161–163°C. after crystallization from benzene:cyclohexane, 1:2.

Elemental analysis for $C_{17}H_{14}Cl_2O_2$:

Calc.: C, 63.57; H, 4.39;

Found: C, 63.24; H, 4.68.

Step F: 2-Methyl-2-phenyl-5-hydroxy-6,7-dichloro-1-indanone

A stirred mixture of 2-methyl-2-phenyl-5-methoxy-6,7-dichloro-1-indanone (4.94 g., 0.015 mole) and pyridine hydrochloride (50 g.) is heated at 175°C. for one hour, then poured into water (500 ml.). The 2-methyl-2-phenyl-5-hydroxy-6,7-dichloro-1-indanone, which separates (2.05 g.) melts at 194–196°C. after recrystallization from ethanol:water, 2:1.

Elemental analysis for $C_{16}H_{12}Cl_2O_2$:

Calc.: C, 62.56; H, 3.94;

Found: C, 62.60; H, 4.11.

Step G: (1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid

A stirred mixture of 2-methyl-2-phenyl-5-hydroxy-6,7-dichloro-1-indanone (2.05 g., 0.0067 mole), potassium carbonate (1.85 g., 0.0134 mole) and ethyl bromoacetate (2.23 g., 0.0134 mole) in dimethylformamide (30 ml.) is warmed at 55–60°C. for 3 hours, then treated with potassium hydroxide (0.97 g., 0.0147 mole) dissolved in a minimum amount of water in methanol (30 ml.) and heated on a steam bath for 2½ hours. The reaction mixture is poured into water (500 ml.) and acidified with 6*N* hydrochloric acid, and the precipitate is collected after trituration with mixtures of ether and petroleum ether and dried to give 1.31 g. of (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid, which melts at 168–169°C. on crystallization from acetic-acid:water, 1:1.

Elemental analysis for $C_{18}H_{14}Cl_2O_4$:

Calc.: C, 59.20; H, 3.86;

Found: C, 58.94; H, 4.20.

EXAMPLE 6.

Where in Example 5, there is substituted for the 2,3-dichloroanisole of Step A

0.1
l.) is
water
rich

5

10

0 g.
for
The
is at

15

20

25

30

35

40

45

50

55

an equivalent amount of 2-chloro-3-methylanisole, 2,3-dimethylanisole and 2-methyl-3-chloroanisole, respectively, the following compounds of this invention are obtained, respectively:

- (1-oxo-2,7-dimethyl-2-phenyl-6-chloro-5-indanyloxy)acetic acid,
- (1-oxo-2,6,7-trimethyl-2-phenyl-5-indanyloxy)acetic acid,
- (1-oxo-2,6-dimethyl-2-phenyl-7-chloro-5-indanyloxy)acetic acid.

EXAMPLE 7.

Preparation of [1-Oxo-2-(4-chlorophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid hemihydrate

Step A: 2-(4-chlorophenyl)-2-methyl-5-methoxy-6,7-dichloro-1-indanone
Potassium *tert*-butoxide (2.81 g., 0.025 mole) dissolved in *tert*-butanol (150 ml.) is added to a refluxing solution of 2-methyl-5-methoxy-6,7-dichloro-1-indanone (4.90 g., 0.02 mole) in a mixture of *tert*-butanol (100 ml.) and benzene (200 ml.), refluxing is continued for 3 hours, then 4,4'-dichlorodiphenyliodonium chloride (11.55 g., 0.03 mole) is added and refluxing is continued for a further 2 hours. The reaction mixture is cooled to 25°C., 100 ml of water added, and the mixture concentrated to dryness *in vacuo* to give 4.30 g. of 2-(4-chlorophenyl)-2-methyl-5-methoxy-6,7-dichloro-1-indanone, which melts at 176—178°C. after crystallization from cyclohexane:benzene, 5:1.

Step B: 2-(4-Chlorophenyl)-2-methyl-5-hydroxy-6,7-dichloro-1-indanone
A stirred mixture of 2-(4-chlorophenyl)-2-methyl-5-methoxy-6,7-dichloro-1-indanone (4.15 g., 0.012 mole) and pyridine hydrochloride (40 g.) is heated at 180°C. for one hour, then poured into water (500 ml.). The 2-(4-chlorophenyl)-2-methyl-5-hydroxy-6,7-dichloro-1-indanone, which separates (3.11 g.), melts at 211—213°C. after crystallization from ethanol:water, 1:1.

Elemental analysis for $C_{16}H_{11}Cl_2O_2$:
Calc.: C, 56.25; H, 3.25;
Found: C, 55.53; H, 3.23.

Step C: [1-oxo-2-(4-chlorophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid hemihydrate

A stirred mixture of 2-(4-chlorophenyl)-2-methyl-5-hydroxy-6,7-dichloro-1-indanone (2.95 g., 0.00863 mole), potassium carbonate (2.26 g., 0.0163 mole) and ethylbromoacetate (2.72 g., 0.0163 mole) in dimethylformamide (50 ml.) is warmed at 55—60°C. for two hours, then treated with water (50 ml.) and 10N sodium hydroxide solution (2.5 ml., 0.025 mole) and heated at 80°C. for one hour. The reaction mixture is added slowly to water (500 ml.) and 12N hydrochloric acid (10 ml.) to precipitate 1.37 g. of [1-oxo-2-(4-chlorophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid hemihydrate, which melts at 141—142°C. after crystallization from acetic-acid:water, 1:1.

Elemental analysis for $C_{18}H_{13}Cl_2O_4 \cdot 1/2H_2O$:
Calc.: C, 52.90; H, 3.45; Cl, 26.03;
Found: C, 52.47; H, 3.45; Cl, 26.11.

EXAMPLE 8.

Preparation of [1-Oxo-2-(4-methoxyphenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid

Step A: 2-Methyl-5-hydroxy-6,7-dichloro-1-indanone
A stirred mixture of 2-methyl-5-methoxy-6,7-dichloro-1-indanone (30.0 g., 0.123 mole) and pyridine hydrochloride (270 g.) is heated at 180°C. for one hour, then poured into water (1500 ml.). The 2-methyl-5-hydroxy-6,7-dichloro-1-indanone, which separates (27.6 g.), melts at 224—230°C. and is used without further purification.

Step B: 2-Methyl-5-benzyloxy-6,7-dichloro-1-indanone
A stirred mixture of 2-methyl-5-hydroxy-6,7-dichloro-1-indanone (27.6 g., 0.12 mole), potassium carbonate (24.9 g., 0.18 mole) and benzyl bromide (21.4 ml., 0.18 mole) in dimethylformamide (100 ml.) is warmed at 55—60°C. for 2 hrs., then

poured into water (1 l.) to precipitate 35.5 g. of 2-methyl-5-benzyloxy-6,7-dichloro-1-indanone, which melts at 153—155°C. after crystallization from benzene:hexane, 3:2.

Elemental analysis for $C_{17}H_{14}Cl_2O_2$:

Calc.: C, 63.57; H, 4.39;

Found: C, 64.28; H, 4.61.

Step C: 2-(4-Methoxyphenyl)-2-methyl-5-benzyloxy-6,7-dichloro-1-indanone

Potassium *tert*-butoxide (8.42 g., 0.075 mole) dissolved in *tert*-butanol (450 ml.) is added to a refluxing solution of 2-methyl-5-benzyloxy-6,7-dichloro-1-indanone (16.1 g., 0.05 mole) in *tert*-butanol (150 ml.)-benzene (600 ml.) and refluxing is continued for 2.5 hours. Then 4,4'-dimethoxydiphenyliodonium chloride (37.66 g., 0.10 mole) is added and refluxing is continued for a further 3 hrs. The reaction mixture is cooled to 25°C., 500 ml. water added, and the mixture concentrated *in vacuo* to give a brown oil which on ether extraction, drying over anhydrous magnesium sulfate, removal of the ether and chromatography of the residue on silica gel with chloroform gives 3.44 g. of 2-(4-methoxyphenyl)-2-methyl-5-benzyloxy-6,7-dichloro-1-indanone, which melts at 115—119°C. and is used without further purification.

Step D: 2-(4-Methoxyphenyl)-2-methyl-5-hydroxy-6,7-dichloro-1-indanone

2-(4-Methoxyphenyl)-2-methyl-5-benzyloxy-6,7-dichloro-1-indanone (3.44 g., 0.008 mole) is catalytically hydrogenated in absolute ethanol (300 ml.) over 5% palladium on carbon (500 mg.) in a Parr apparatus at 25°C. for 4 hrs. The reaction mixture is filtered and concentrated *in vacuo* to give 2.6 g. of 2-(4-methoxyphenyl)-2-methyl-5-hydroxy-6,7-dichloro-1-indanone, which melts at 149—156°C. and is used without further purification.

Step E: [1-Oxo-2-(4-methoxyphenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid

A stirred mixture of 2-(4-methoxyphenyl)-2-methyl-5-hydroxy-6,7-dichloro-1-indanone (2.6 g., 0.0077 mole), potassium carbonate (2.14 g., 0.0154 mole) and ethyl bromoacetate (2.58 g., 0.0154 mole) in dimethylformamide (60 ml.) is warmed at 55—60°C. for 2.5 hrs., then treated with water (60 ml.) and 10*N* sodium hydroxide solution (3 ml., 0.03 mole) and heated at 100°C. for one hour. The reaction mixture is added slowly to crushed ice-water (600 ml.) and 12*N* hydrochloric acid (20 ml.) to precipitate 1.69 g. of [1-oxo-2-(4-methoxyphenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid, which melts at 173—175°C. after crystallization from nitromethane.

Elemental analysis for $C_{19}H_{16}Cl_2O_5$:

Calc.: C, 57.74; H, 4.08;

Found: C, 57.35; H, 4.31.

EXAMPLE 9.

Preparation of [1-Oxo-2-(4-hydroxyphenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid

A stirred mixture of [1-oxo-2-(4-methoxyphenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid (1.80 g., 0.0046 mole), Example 8, Step E, 48% hydrobromic acid (50 ml.) and acetic acid (50 ml.) is heated at reflux for one hour, then poured into crushed ice-water (800 ml.) to precipitate 900 mg. of [1-oxo-2-(4-hydroxyphenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid, which melts at 220—222°C. after crystallization from acetic acid:water, 1:1, and nitromethane.

Elemental analysis for $C_{18}H_{14}Cl_2O_5 \cdot 1/3CH_3NO_2$:

Calc.: C, 54.84; H, 3.77; N, 1.16;

Found: C, 54.38; H, 3.93; N, 0.94.

EXAMPLE 10.

Ethyl (1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetate

To a solution of (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid (1.0 g.), obtained from Example 5, in ethanol (10 ml.) is added boron trifluoride etherate (1.0 ml.). The reaction mixture is refluxed for half an hour, treated with water and cooled to afford the ethyl (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetate.

EXAMPLE 11.

N-Ethyl-(1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetamide

A solution of (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid (1.0 g.) obtained from Example 5 and thionyl chloride (0.5 ml.) in benzene (20 ml.) is refluxed for one hour. The solvent is distilled at reduced pressure and the residue is treated with benzene (10 ml.) and ethylamine (1 ml.). After two hours at 25°C. the reaction mixture is poured into water and extracted with ether; the ethereal extract is washed first with diluted hydrochloric acid then with aqueous sodium bicarbonate. The ethereal solution is dried over magnesium sulfate and evaporated at reduced pressure to afford the desired N-ethyl-(1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetamide.

EXAMPLE 12.

Preparation of [1-Oxo-2-(4-fluorophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid

Step A: 2-(4-Fluorophenyl)-2-methyl-5-methoxy-6,7-dichloro-1-indanone

Potassium *tert*-butoxide (3.38 g., 0.03 mole) dissolved in *tert*-butanol (150 ml.) is added to a refluxing solution of 2-methyl-5-methoxy-6,7-dichloro-1-indanone (4.90 g., 0.02 mole) in *tert*-butanol (50 ml.) and benzene (200 ml.). Refluxing is continued for 3 hours, then 4,4'-difluorodiphenyliodonium chloride (10.58 g., 0.03 mole) is added and refluxing is continued for a further 2½ hours. The reaction mixture is cooled to 25°C., 100 ml. of water added, and the mixture concentrated to dryness *in vacuo* to give 1.24 g. of 2-(4-fluorophenyl)-2-methyl-5-methoxy-6,7-dichloro-1-indanone, which melts at 163–170°C. on treatment with ether-hexane and is used without further purification.

Step B: 2-(4-Fluorophenyl)-2-methyl-5-hydroxy-6,7-dichloro-1-indanone

A stirred mixture of 2-(4-fluorophenyl)-2-methyl-5-methoxy-6,7-dichloro-1-indanone (1.2 g., 0.00354 mole) and pyridine hydrochloride (12 g.) is heated at 180°C. for one hour, then poured into water (500 ml.). The 2-(4-fluorophenyl)-2-methyl-5-hydroxy-6,7-dichloro-1-indanone melts at 193–200°C. and is used without further purification.

Step C: [1-Oxo-2-(4-fluorophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid

A stirred mixture of 2-(4-fluorophenyl)-2-methyl-5-hydroxy-6,7-dichloro-1-indanone (1.04 g., 0.0032 mole), potassium carbonate (0.885 g., 0.0064 mole) and ethyl bromoacetate (1.07 g., 0.0064 mole) in dimethylformamide (30 ml.) is warmed at 55–60°C. for 3 hours, then treated with water (30 ml.) and 10*N* sodium hydroxide solution (1 ml., 0.01 mole), and heated at 80°C. for one hour. The reaction mixture is added slowly to water (500 ml.) and 12*N* hydrochloric acid (10 ml.) to precipitate 450 mg. of [1-oxo-2-(4-fluorophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid, which melts at 150–156°C. after crystallization from ethyl-acetate:hexane, 1:3.

Elemental analysis for $C_{18}H_{13}Cl_2FO_4$:

Calc.: C, 56.42; H, 3.42; Cl, 18.50;

Found: C, 56.30; H, 3.65; Cl, 18.57.

EXAMPLE 13.

Preparation of (1-Oxo-2,2-diphenyl-6,7-dichloro-5-indanyloxy)acetic acid

Step A: 2,2-Diphenyl-5-methoxy-6,7-dichloro-1-indanone

Potassium *tert*-butoxide (7.0 g., 0.0624 mole) dissolved in *tert*-butanol (500 ml.) is added to a mixture of 2-phenyl-5-methoxy-6,7-dichloro-1-indanone (9.59 g., 0.0312 mole), diphenyliodonium chloride (39.6 g., 0.125 mole), *tert*-butanol (1500 ml.) and benzene (500 ml.) at 70°C. during one hour, then stirred at 70°C. for 2 hours. The reaction mixture is concentrated *in vacuo* to ¼ of its volume, unreacted iodonium salt filtered off, and the remaining liquid concentrated to dryness to give 5.71 g. of 2,2-diphenyl-5-methoxy-6,7-dichloro-1-indanone, which melts at 172–174°C. after crystallization from cyclohexane.

Elemental analysis for $C_{22}H_{16}Cl_2O_2$:

Calc.: C, 68.94; H, 4.21;

Found: C, 68.99; H, 4.34.

Step B: 2,2-Diphenyl-5-hydroxy-6,7-dichloro-1-indanone

A stirred mixture of 2,2-diphenyl-5-methoxy-6,7-dichloro-1-indanone (5.5 g., 0.014 mole) and pyridine hydrochloride (55 g.) is heated at 175°C. for half an hour, then poured into water (500 ml.). The 2,2-diphenyl-5-hydroxy-6,7-dichloro-1-indanone, which separates (4.94 g.), melts at 207—213°C.

Elemental analysis for $C_{21}H_{14}Cl_2O_2$:

Calc.: C, 68.31; H, 3.82;

Found: C, 67.86; H, 3.88.

Step C: (1-Oxo-2,2-diphenyl-6,7-dichloro-5-indanyloxy)acetic acid

A stirred mixture of 2,2-diphenyl-5-hydroxy-6,7-dichloro-1-indanone (4.9 g., 0.0133 mole), potassium carbonate (3.68 g., 0.0266 mole) and ethyl bromoacetate (4.45 g., 0.0266 mole) in dimethylformamide (150 ml.) is warmed at 55—60°C. for 3.5 hours, then treated with water (150 ml.) and 10N sodium hydroxide solution (7.5 ml., 0.075 mole) and heated at 90°C for 1.5 hrs. The reaction mixture is added slowly to water (1 l.) and 12N hydrochloric acid (30 ml.) to precipitate 3.60 g. of (1-oxo-2,2-diphenyl-6,7-dichloro-5-indanyloxy)acetic acid, which melts at 251—252°C. after crystallization first from acetic acid and then from nitromethane.

Elemental analysis for $C_{23}H_{16}Cl_2O_4$:

Calc.: C, 64.65; H, 3.77; Cl, 16.59;

Found: C, 64.69; H, 3.94; Cl, 16.73.

EXAMPLE 14.**Preparation of (1-Oxo-2,3-diphenyl-2-methyl-6,7-dichloro-5-indanyloxy)acetic acid****Step A: 2',3'-Dichloro-4'-methoxypropionophenone**

A stirred mixture of 2,3-dichloroanisole (177.0 g., 1.0 mole) and propionyl chloride (101.8 g., 1.1 mole) in methylene chloride (600 ml.) is cooled to 5°C. and treated with aluminum chloride (146.7 g., 1.1 mole) during a 1½ hour period. The reaction mixture is allowed to warm to 25°C. and after 16 hours is poured into ice-water (2 l.) and concentrated hydrochloric acid (200 ml.). The organic phase is washed with 10% sodium hydroxide solution and saturated salt solution, and dried over magnesium sulfate. After evaporation of the solvent, the product is crystallized from hexane to give 124.5 g. (53%) of 2',3'-dichloro-4'-methoxypropionophenone, which melts at 51—54°C.

Step B: 2,3-Dichloro-4-(2-benzylidenepropionyl)anisole

To a mixture of 2',3'-dichloro-4'-methoxypropionophenone (124.5 g., 0.53 mole) and benzaldehyde (54.4 ml., 0.53 mole) dissolved in ethanol (1 l.) is added dropwise 20% sodium hydroxide solution (117.0 ml., 0.59 mole). The product begins to precipitate after three quarters of the base has been added. After two hours at 25°C. the solid product is collected by suction filtration to give 163.2 g. (95%) of 2,3-dichloro-4-(2-benzylidenepropionyl)anisole, which melts at 137.5—139°C. after crystallization from ethanol.

Elemental analysis for $C_{17}H_{14}Cl_2O_2$:

Calc.: C, 63.57; H, 4.39;

Found: C, 63.69; H, 4.49.

Step C: 2-Methyl-3-phenyl-5-methoxy-6,7-dichloro-1-indanone

2,3-Dichloro-4-(2-benzylidenepropionyl)anisole (100 g., 0.32 mole) and trifluoroacetic acid (400 ml.) are heated at gentle reflux for 67 hours. The trifluoroacetic acid is removed, the oily residue triturated with ether to give 80.0 g. of 2-methyl-3-phenyl-5-methoxy-6,7-dichloro-1-indanone, which on crystallization from benzene melts at 155—157°C.

Elemental analysis for $C_{17}H_{14}Cl_2O_2$:

Calc.: C, 63.57; H, 4.39;

Found: C, 63.17; H, 4.59.

5.5 g.,
1 hour,
oro-1-

5

4.9 g.,
acetate
C. for
olution
added
of (1-
ts at
nitro-

10

15

20

25

30

35

40

nole)
wise
ns to
rs at
%) of
9°C.

l tri-
dro-
of 2-
ation

50

Step D: 2,3-Diphenyl-2-methyl-5-methoxy-6,7-dichloro-1-indanone

Sodium methoxide (2.4 g., 0.045 mole) is added portionwise to a stirred mixture of 2-methyl-3-phenyl-5-methoxy-6,7-dichloro-1-indanone (6.44 g., 0.02 mole), diphenyliodonium chloride (31.6 g., 0.1 mole), dry dimethylformamide (200 ml.) and benzene (200 ml.) at 70°C. under nitrogen, and heating at 70°C. is continued for 2 hours. The reaction mixture is poured into water (1.5 l.) and the benzene layer separated, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give 2.48 g. of 2,3-diphenyl-2-methyl-5-methoxy-6,7-dichloro-1-indanone after trituration with hexane. This material, which melts at 197—207°C., is used without further purification.

Step E: 2,3-Diphenyl-2-methyl-5-hydroxy-6,7-dichloro-1-indanone

A stirred mixture of 2,3-diphenyl-2-methyl-5-methoxy-6,7-dichloro-1-indanone (2.48 g., 0.0065 mole) and pyridine hydrochloride (25 g.) is heated at 175°C. for one hour, then poured into water (500 ml.). The 2,3-diphenyl-2-methyl-5-hydroxy-6,7-dichloro-1-indanone, which separates (2.24 g.), melts at 238—244°C. and is used without further purification.

Step F: (1-Oxo-2,3-diphenyl-2-methyl-6,7-dichloro-5-indanyloxy)acetic acid

A stirred mixture of 2,3-diphenyl-2-methyl-5-hydroxy-6,7-dichloro-1-indanone (2.24 g., 0.00585 mole), potassium carbonate (1.62 g., 0.0117 mole) and ethyl bromoacetate (1.96 g., 0.0117 mole) in dimethylformamide (100 ml.) is warmed at 55—60°C. for 3 hours, then treated with water (100 ml.) and 10N sodium hydroxide solution (5 ml., 0.05 mole) and heated at 90°C. for 1.5 hours. The reaction mixture is added slowly to water (1 l.) and 12N hydrochloric acid (10 ml.) to precipitate 1.14 g. of (1-oxo-2,3-diphenyl-2-methyl-6,7-dichloro-5-indanyloxy)acetic acid, which melts at 203—205°C. after crystallization from nitromethane.

Elemental analysis for $C_{24}H_{18}Cl_2O_4$:

Calc.: C, 65.32; H, 4.11;

Found: C, 65.30; H, 4.19.

EXAMPLE 15.

Preparation of (1-Oxo-2-ethyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid

Step A: 2-Ethyl-2-phenyl-5-methoxy-6,7-dichloro-1-indanone

Sodium methoxide (1.24 g., 0.023 mole) is added portionwise to a stirred mixture of 2-phenyl-5-methoxy-6,7-dichloro-1-indanone (4.61 g., 0.015 mole), indoethane (15.5 ml., 0.15 mole), benzene (60 ml.) and dimethylformamide (60 ml.) under nitrogen in an ice-water bath. The reaction mixture is left to come to ambient temperature over one hour, then poured into water (1 l.), and the benzene layer is separated, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give 3.23 g. of 2-ethyl-2-phenyl-5-methoxy-6,7-dichloro-1-indanone, which melts at 139—141°C. on crystallization from benzene:hexane, 1:1.

Elemental analysis for $C_{18}H_{16}Cl_2O_2$:

Calc.: C, 64.49; H, 4.81;

Found: C, 64.73; H, 4.99.

Step B: 2-Ethyl-2-phenyl-5-hydroxy-6,7-dichloro-1-indanone

A stirred mixture of 2-ethyl-2-phenyl-5-methoxy-6,7-dichloro-1-indanone (3.01 g., 0.009 mole) and pyridine hydrochloride (35 g.) is heated at 175°C. for half an hour, then poured into water (350 ml.). The 2-ethyl-2-phenyl-5-hydroxy-6,7-dichloro-1-indanone, which separates (2.64 g.), melts at 177—179°C.

Elemental analysis for $C_{17}H_{14}Cl_2O_2$:

Calc.: C, 63.57; H, 4.39;

Found: C, 63.73; H, 4.81.

Step C: (1-Oxo-2-ethyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid

A stirred mixture of 2-ethyl-2-phenyl-5-hydroxy-6,7-dichloro-1-indanone (2.6 g., 0.008 mole), potassium carbonate (2.24 g., 0.016 mole) and ethyl bromoacetate (2.71 g., 0.016 mole) in dimethylformamide (40 ml.) is warmed at 55—60°C. for 2.5 hours, then treated with water (40 ml.) and 10N sodium hydroxide solution (3 ml., 0.03 mole) and heated at 100°C. for one hour. The reaction mixture is added

slowly to water (600 ml.) and 12*N* hydrochloric acid (10 ml.) to give a gummy residue which, on ether extraction, drying and concentrating *in vacuo* gives 2.16 g. of (1-oxo-2-ethyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid, which melts at 187–189°C.

5 Elemental analysis for $C_{19}H_{16}Cl_2O_4$:
 Calc.: C, 60.18; H, 4.25;
 Found: C, 59.76; H, 4.24.

EXAMPLE 16.

10 Preparation of (1-Oxo-2-cyclopentyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid

Step A: 2-Cyclopentyl-2-phenyl-5-methoxy-6,7-dichloro-1-indanone
 Sodium methoxide (1.63 g., 0.03 mole) is added portionwise to a stirred mixture of 2-phenyl-5-methoxy-6,7-dichloro-1-indanone (4.61 g., 0.015 mole), cyclopentyl bromide (16 ml., 0.15 mole), benzene (60 ml.) and dimethyl formamide (60 ml.) under nitrogen at 25°C. The reaction mixture is stirred at 25°C. for 16
 15 hours, then poured into water (1 l.) and the benzene layer is separated, dried over anhydrous magnesium sulfate and concentrated *in vacuo* leaving a red-brown oily residue, which is chromatographed with chloroform on silica gel to give 1.42 g. of 2-cyclopentyl-2-phenyl-5-methoxy-6,7-dichloro-1-indanone, which melts at
 20 105–108°C.

 Elemental analysis for $C_{21}H_{20}Cl_2O_2$:
 Calc.: C, 67.21; H, 5.37;
 Found: C, 66.88; H, 5.53.

Step B: 2-Cyclopentyl-2-phenyl-5-hydroxy-6,7-dichloro-1-indanone
 25 A stirred mixture of 2-cyclopentyl-2-phenyl-5-methoxy-6,7-dichloro-1-indanone (1.40 g., 0.0037 mole) and pyridine hydrochloride (14 g.) is heated at 175°C. for half an hour, then poured into water (400 ml.). The 2-cyclopentyl-2-phenyl-5-hydroxy-6,7-dichloro-1-indanone, which separates (1.1 g.), melts at 161–170°C. on crystallization from butyl chloride:chloroform, 5:1.

30 Elemental analysis for $C_{20}H_{18}Cl_2O_2$:
 Calc.: C, 66.49; H, 5.02;
 Found: C, 65.52; H, 5.03.

Step C: (1-Oxo-2-cyclopentyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid
 35 A stirred mixture of 2-cyclopentyl-2-phenyl-5-hydroxy-6,7-dichloro-1-indanone (1.10 g., 0.003 mole), potassium carbonate (0.85 g., 0.006 mole) and ethyl bromoacetate (1.02 g., 0.006 mole) in dimethylformamide (20 ml.) is warmed at 55–60°C. for 3 hours, then treated with water (20 ml.) and 10*N* sodium hydroxide solution (1.2 ml., 0.012 mole) and heated at 100°C. for one hour. The reaction
 40 mixture is added slowly to water (300 ml.) and 12*N* hydrochloric acid (5 ml.) to precipitate 680 mg. of (1-oxo-2-cyclopentyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid, which melts at 184–186°C. after crystallization from nitromethane.

 Elemental analysis for $C_{22}H_{20}Cl_2O_4$:
 Calc.: C, 63.02; H, 4.81;
 Found: C, 62.59; H, 4.86.

EXAMPLE 17.

45 Preparation of [1-Oxo-2-methyl-2-(4-nitrophenyl)-6,7-dichloro-5-indanyloxy]acetic acid

Step A: 2-Methyl-2-(4-nitrophenyl)-5-methoxy-6,7-dichloro-1-indanone
 50 Amyl nitrate (40 ml.) is added in 10-ml. increments at two-hour intervals to 2-methyl-2-phenyl-5-methoxy-6,7-dichloro-1-indanone (9.36 g., 0.03 mole) in polyphosphoric acid (150 g.) at 50–60°C. with stirring. The total heating period is 8 hours. The reaction mixture is treated with crushed ice-water to precipitate 4.82 g. of 2-methyl-2-(4-nitrophenyl)-5-methoxy-6,7-dichloro-1-indanone, which melts at 179–180°C. after crystallization from butyl chloride.

55 Elemental analysis for $C_{17}H_{13}Cl_2NO_4$:
 Calc.: C, 55.76; H, 3.58; N, 3.82;
 Found: C, 55.83; H, 3.66; N, 3.85.

a gummy
res 2.16 g.
melts at

5

10

a stirred
5 mole),
mamide
2. for 16
ied over
own oily
1.42 g.
melts at

15

20

25

loro-1-
ated at
entyl-2-
melts at

30

id
loro-1-
d ethyl
med at
roxide
action
ml.) to
(oxy)-
thane.

35

40

s to 2-
poly-
d is 8
.82 g.
elts at

50

55

Step B: 2-Methyl-2-(4-nitrophenyl)-5-hydroxy-6,7-dichloro-1-indanone

A stirred mixture of 2-methyl-2-(4-nitrophenyl)-5-methoxy-6,7-dichloro-1-indanone (4.82 g., 0.013 mole) and pyridine hydrochloride (50 g.) is heated at 175°C. for half an hour, then poured into crushed ice-water (1 l.). The 2-methyl-2-(4-nitrophenyl)-5-hydroxy-6,7-dichloro-1-indanone, which separates (4.42 g.), melts at 268—270°C. after crystallization from ethanol.

Elemental analysis for $C_{16}H_{11}Cl_2NO_4$:

Calc.: C, 54.57; H, 3.15; N, 3.98;

Found: C, 54.18; H, 3.27; N, 4.66.

10

Step C: [1-Oxo-2-methyl-2-(4-nitrophenyl)-6,7-dichloro-5-indanyloxy]acetic acid

A stirred mixture of 2-methyl-2-(4-nitrophenyl)-5-hydroxy-6,7-dichloro-1-indanone (4.4 g., 0.0126 mole), potassium carbonate (3.49 g., 0.0252 mole) and ethyl bromoacetate (4.21 g., 0.0252 mole) in dimethylformamide (150 ml.) is warmed at 55—60°C. for 3 hours, then treated with water (150 ml.) and 10N sodium hydroxide solution (7.5 ml., 0.075 mole) and heated at 100°C. for 1.5 hours. The reaction mixture is added slowly to water (1 l.) and 12N hydrochloric acid (15 ml.) to precipitate 2.44 g. of [1-oxo-2-methyl-2-(4-nitrophenyl)-6,7-dichloro-5-indanyloxy]acetic acid, which melts at 202—205°C. after crystallization from nitromethane.

20

Elemental analysis for $C_{18}H_{13}Cl_2NO_6$:

Calc.: C, 52.70; H, 3.19; N, 3.41;

Found: C, 52.72; H, 3.16; N, 3.30.

EXAMPLE 18.

Preparation of [1-Oxo-2-(4-aminophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid

[1-Oxo-2-methyl-2-(4-nitrophenyl)-6,7-dichloro-5-indanyloxy]acetic acid (6.11 g., 0.015 mole) in absolute ethanol (250 ml.) and 36N sulfuric acid (2 ml.) is catalytically hydrogenated over 5% palladium on carbon (500 mg.) in a Parr apparatus. After one hour, the reaction mixture is filtered, then concentrated *in vacuo* to a 50 ml. volume. Water (200 ml.) is added to precipitate the ethyl ester, which is hydrolysed by refluxing in ethanol (200 ml.), 10N sodium hydroxide solution (4.5 ml., 0.045 mole) and water (100 ml.) for 1.5 hours. The reaction mixture is cooled, concentrated to $\frac{1}{2}$ its volume, filtered, and then neutralized with 6N hydrochloric acid to precipitate 1.09 g. of [1-oxo-2-(4-aminophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid, which melts at 235—236°C. dec.

35

Elemental analysis for $C_{18}H_{15}Cl_2NO_4$:

Calc.: C, 56.86; H, 3.98; N, 3.68;

Found: C, 56.46; H, 4.04; N, 3.62.

EXAMPLE 19.

Preparation of 5-(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy-methyl)tetrazole

Step A: (1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetonitrile

2-Methyl-2-phenyl-5-hydroxy-6,7-dichloro-1-indanone (4.61 g., 0.015 mole), chloroacetonitrile (1.13 g., 0.015 mole), potassium carbonate (2.08 g., 0.015 mole), potassium iodide (0.25 g., 0.0015 mole) and acetone (75 ml.) are heated at reflux for 23 hours. The reaction mixture is cooled to 25°C. and concentrated to dryness *in vacuo* to give an oily residue which, on trituration with water, gives 5.12 g. of (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetonitrile, which melts at 163—165°C. on crystallization from cyclohexane:benzene, 5:1.

45

50

Elemental analysis for $C_{18}H_{13}Cl_2NO_2$:

Calc.: C, 62.45; H, 3.78; N, 4.05;

Found: C, 63.06; H, 4.03; N, 4.03.

Step B: 5-(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxymethyl)tetrazole

(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetonitrile (4.87 g., 0.014 mole), sodium azide (1.09 g., 0.0168 mole), ammonium chloride (0.90 g., 0.0168 mole) and dimethylformamide (30 ml.) are heated at 80°C. for 2 $\frac{1}{2}$ hrs. The reaction mixture is poured into water (500 ml.) and the solution is filtered and

55

55

acidified with 6*N* hydrochloric acid to precipitate 2.60 g. of 5-(1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxymethyl)tetrazole, which melts at 227–229°C. after crystallization from ethanol.

5 Elemental analysis for $C_{15}H_{14}Cl_2N_4O_2$:
 Calc.: C, 55.54; H, 3.63; N, 14.39;
 Found: C, 55.29; H, 3.90; N, 14.40.

EXAMPLE 20.

Preparation of [1-Oxo-2-(4-bromophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid

10 Step A: 2,3-Dichloro-4-(4-bromophenyl)-acetylanisole
 To a stirred mixture of 2,3-dichloroanisole (73.5 g., 0.414 mole), and 4-bromophenylacetyl chloride (105 g., 0.456 mole) and carbon disulfide (300 ml.) is added portionwise aluminium chloride (60.9 g., 0.456 mole) with cooling at 0–5°C. The reaction mixture is left at 25°C. for 17 hours, then flushed with nitrogen, and the solid residue treated with crushed ice and 12*N* hydrochloric acid (80 ml.) to give 147.7 g. of 2,3-dichloro-4-(4-bromophenyl)acetylanisole, which melts at 163–164.5°C. after crystallization from benzene:hexane, 1:1.

15 Elemental analysis for $C_{15}H_{11}BrCl_2O_2$:
 Calc.: C, 48.16; H, 2.96;
 Found: C, 48.38; H, 3.10.

20 Step B: 2',3'-Dichloro-4'-methoxy-2-(4-bromophenyl)acrylophenone

25 To a suspension of 2,3-dichloro-4-(4-bromophenyl)acetyl anisole (142.5 g., 0.38 mole) in bis-dimethylaminomethane (325 ml.) under nitrogen is added dropwise acetic anhydride (325 ml.) with cooling to maintain the reaction mixture temperature below 40°C. The reaction mixture is stirred at 25°C. for one hour, then poured into crushed ice-water (4 l.) to precipitate 143 g. of 2',3'-dichloro-4'-methoxy-2-(4-bromophenyl)acrylophenone, which melts at 110–116°C. after crystallization from benzene:hexane, 1:5.

30 Elemental analysis for $C_{18}H_{11}BrCl_2O_2$:
 Calc.: C, 49.78; H, 2.87;
 Found: C, 49.73; H, 2.88.

35 Step C: 2-(4-Bromophenyl)-5-methoxy-6,7-dichloro-1-indanone

2',3'-Dichloro-4'-methoxy-2-(4-bromophenyl)acrylophenone (143 g., 0.37 mole) dissolved in dichloromethane (2 l.) is dripped into cold 36*N* sulfuric acid (1 l.) and dichloromethane (1 l.) in an ice bath over 4 hours. After being stirred for an additional half hour, the reaction mixture is slowly added to crushed ice and the dichloromethane layer is separated, washed with saturated salt solution and concentrated *in vacuo* to give 134.8 g. of 2-(4-bromophenyl)-5-methoxy-6,7-dichloro-1-indanone, which melts at 202–203°C. after trituration with water followed by crystallization from benzene:hexane, 1:1.

40 Elemental analysis for $C_{18}H_{11}BrCl_2O_2$:
 Calc.: C, 49.78; H, 2.87;
 Found: C, 50.46; H, 3.07.

45 Step D: 2-(4-Bromophenyl)-2-methyl-5-methoxy-6,7-dichloro-1-indanone

Sodium methoxide (28.4 g., 0.522 mole) is added to a stirred mixture of 2-(4-bromophenyl)-5-methoxy-6,7-dichloro-1-indanone (134.6 g., 0.348 mole), iodomethane (217 ml., 3.48 mole), dry benzene (1700 ml.) and dry dimethylformamide (1700 ml.) under nitrogen in an ice-water bath. The reaction mixture is left to come to ambient temperature over 2 hours, then poured into water (8 l.) to precipitate 92.2 g. of 2-(4-bromophenyl)-2-methyl-5-methoxy-6,7-dichloro-1-indanone, m.p. 200–203°C., which is not soluble in the benzene present.

50 Elemental analysis for $C_{19}H_{13}BrCl_2O_2$:
 Calc.: C, 51.03; H, 3.28;
 Found: C, 50.71; H, 3.24.

nethyl-2-
-229°C.

5

10

and 4-
0 ml.) is
oling at
ed with
ric acid
, which

15

20

12.5 g.,
added
reaction
25°C.
of 2',3'-
is at

25

30

0.37
acid (1
for an
d the
con-
ro-1-
ed by

35

40

2-(4-
mole),
ethyl-
ure is
l.) to
ro-1-

45

50

Step E: 2-(4-Bromophenyl)-2-methyl-5-hydroxy-6,7-dichloro-1-indanone

A stirred mixture of 2-(4-bromophenyl)-2-methyl-5-methoxy-6,7-dichloro-1-indanone (5.0 g., 0.0125 mole) and pyridine hydrochloride (50 g.) is heated at 185°C. for one hour, then poured into crushed ice-water (500 ml.). The 2-(4-bromophenyl)-2-methyl-5-hydroxy-6,7-dichloro-1-indanone, which separates (4.68 g.), melts at 221—223°C. after crystallization from ethanol.

Elemental analysis for $C_{16}H_{11}BrCl_2O_2$:

Calc.: C, 49.78; H, 2.87;

Found: C, 49.18; H, 2.87.

10

Step F: [1-Oxo-2-(4-bromophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid

A stirred mixture of 2-(4-bromophenyl)-2-methyl-5-hydroxy-6,7-dichloro-1-indanone (4.48 g., 0.0116 mole), potassium carbonate (3.88 g., 0.0232 mole) and ethyl bromoacetate (3.21 g., 0.0232 mole) in dimethylformamide (100 ml.) is warmed at 55—60°C. for 3 hours, then treated with water (100 ml.) and 10N sodium hydroxide solution (5 ml., 0.05 mole) and heated at 100°C. for 2 hours. The reaction mixture is added slowly to crushed ice-water (1500 ml.) and 12N hydrochloric acid (50 ml.) to precipitate 3.24 g. of [1-oxo-2-(4-bromophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid, which melts at 171—172°C. after crystallization from nitromethane followed by acetic-acid:water, 3:2.

15

20

Elemental analysis for $C_{16}H_{11}BrCl_2O_4$:

Calc.: C, 48.68; H, 2.95;

Found: C, 48.64; H, 2.93.

20

EXAMPLE 21.

Preparation of [1-Oxo-2-(4-cyanophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid

25

Step A: 2-(4-Cyanophenyl)-2-methyl-5-methoxy-6,7-dichloro-1-indanone

2-(4-Bromophenyl)-2-methyl-5-methoxy-6,7-dichloro-1-indanone (8.00 g., 0.02 mole), cuprous cyanide (3.94 g., 0.04 mole) and dimethylformamide (100 ml.) are heated at reflux for 8 hours, added to warm sodium cyanide solution (3 g. in 400 ml. water) and extracted with benzene. The benzene solution is dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give an oily residue. Chromatographing with chloroform on silica gel gives 1.13 g. of 2-(4-cyanophenyl)-2-methyl-5-methoxy-6,7-dichloro-1-indanone, which melts at 161—163°C. after crystallization from benzene:hexane, 2:1.

30

35

Elemental analysis for $C_{15}H_{11}Cl_2NO_2$:

Calc.: C, 62.45; H, 3.78; N, 4.05;

Found: C, 61.37; H, 3.68; N, 3.73.

35

Step B: 2-(4-Cyanophenyl)-2-methyl-5-hydroxy-6,7-dichloro-1-indanone

A stirred mixture of 2-(4-cyanophenyl)-2-methyl-5-methoxy-6,7-dichloro-1-indanone (2.08 g., 0.006 mole) and pyridine hydrochloride (20 g.) is heated at 185°C. for 2 hours, then poured into ice-water (300 ml.). The 2-(4-cyanophenyl)-2-methyl-5-hydroxy-6,7-dichloro-1-indanone, which separates (1.89 g.), melts at 189—196°C. and is used without further purification.

40

45

Step C: [1-Oxo-2-(4-cyanophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid

A stirred mixture of 2-(4-cyanophenyl)-2-methyl-5-hydroxy-6,7-dichloro-1-indanone (1.8 g., 0.0054 mole), potassium carbonate (1.5 g., 0.0109 mole) and ethyl bromoacetate (1.8 g., 0.0109 mole) in dimethylformamide (60 ml.) is warmed at 55—60°C. for 3 hours, then treated with water (60 ml.) and 10N sodium hydroxide solution (3 ml., 0.03 mole) and heated at 100°C. for 1.5 hours. The reaction mixture is added slowly to ice-water (300 ml.) and 12N hydrochloric acid (5 ml.) to precipitate 160 mg. of [1-oxo-2-(4-cyanophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid which melts at 184—5°C. after crystallization from acetic acid:water, 1:1.

50

55

Elemental analysis for $C_{15}H_{11}Cl_2NO_4 \cdot H_2O$:

Calc.: C, 55.90; H, 3.70; N, 3.43;

Found: C, 55.77; H, 3.53; N, 4.00.

55

EXAMPLE 22.

Preparation of [1-Oxo-2-methyl-2-(4-sulfamoylphenyl)-6,7-dichloro-5-indanyloxy]acetic acid

Step A: [1-Oxo-2-(4-chlorosulfonylphenyl)-2-methyl-6,7-dichloro-5-indanyloxy]-acetic acid

(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid (0.50 g., 0.0014 mole) is added portionwise with stirring to chlorosulfonic acid (5 ml.) in an ice-water bath. The reaction mixture is stirred at 0°C. for 2 hours, left to come to ambient temperature for 2 hours, then slowly added to crushed ice to precipitate 0.51 g. of [1-oxo-2-(4-chlorosulfonylphenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid, which melts at 209—210°C. after crystallization from acetic acid:water, 3:2.

Elemental analysis for $C_{18}H_{13}Cl_2O_4S$:

Calc.: C, 46.62; H, 2.83; Cl, 22.94;

Found: C, 46.67; H, 2.79; Cl, 22.59.

Step B: [1-Oxo-2-methyl-2-(4-sulfamoylphenyl)-6,7-dichloro-5-indanyloxy]acetic acid

[1-Oxo-2-(4-chlorosulfonylphenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid (2.0 g., 0.0043 mole) is added portionwise to liquid ammonia with stirring. The ammonia is left to evaporate (3 hours). The residue is dissolved in water (400 ml.), filtered, and acidified with 12N hydrochloric acid to precipitate 780 mg. of [1-oxo-2-methyl-2-(4-sulfamoylphenyl)-6,7-dichloro-5-indanyloxy]acetic acid, which melts at 258—260°C. after crystallization from acetic acid.

Elemental analysis for $C_{18}H_{15}Cl_2NO_6S \cdot 1/4 CH_3CO_2H$:

Calc.: C, 48.38; H, 3.51; N, 3.05;

Found: C, 48.15; H, 3.52; N, 2.86.

EXAMPLE 23.

Process for preparing (1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid (See British Pat. 1,328,528)

A mixture of 1-(1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)-2-nitroethane (3 g.) and 6N hydrochloric acid (100 ml.) is refluxed for 16 hours, cooled and extracted with ether. The ethereal layer is washed with water and extracted with dilute aqueous sodium bicarbonate which upon acidification affords 2.0 g. of (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid which melts at 168—169°C.

EXAMPLE 24.

Process for preparing (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid

To a suspension of sodium hydride (0.24 g., 0.01 mole) in 1,2-dimethoxyethane (10 ml.) is added a solution of 2-methyl-2-phenyl-5-hydroxy-6,7-dichloro-1-indanone (3.07 g., 0.01 mole) in 1,2-dimethoxyethane (10 ml.) over a 15-minute period. When the evolution of hydrogen ceases, diethyl-2-bromomalonate (2.39 g., 0.01 mole) is added and the mixture is refluxed for 1 hour. The solvent is distilled at reduced pressure. The residual diethyl-2-(1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)malonate is dissolved in ethanol (50 ml.). Water (50 ml.) and sodium bicarbonate (2.5 g.) are added and the mixture is refluxed for four hours, cooled, acidified, extracted with ether, washed with water, and dried over magnesium sulfate.

The ether is evaporated at reduced pressure to give crude 2-(1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)-malonic acid, which is heated at 150°C. until evolution of carbon dioxide ceases, affording (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid, which melts at 168—169°C. after recrystallization from nitromethane.

EXAMPLE 25.

Process for preparing (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid

A mixture of (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetonitrile (3.0 g.), from Example 19, Step A, acetic acid (20 ml.), water (5 ml.) and concentrated sulfuric acid (5 ml.) is refluxed for 2 hours then poured into ice-water

(100 ml.) affording 2.5 g. of (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)-acetic acid, which melts at 168—169°C. after recrystallization from acetic acid.

EXAMPLE 26.

(1,2-Dichloro-5 α ,5,6,7,8,8 α -hexahydro-8 α -phenyl-9-oxofluoren-3-yl)oxy)acetic acid

Step A: Cyclohexyl(2,3-dichloro-4-methoxyphenyl) ketone

A stirred mixture of 2,3-dichloroanisole (88.5 g., 0.5 mole) and cyclohexanecarbonyl chloride (81 g., 0.55 mole) in methylene chloride (400 ml.) is cooled to 5°C. and treated with aluminum chloride (74 g., 0.55 mole) during half an hour. The reaction mixture is allowed to warm to 25°C. and after 16 hours is poured into ice-water (1 l.) and hydrochloric acid (200 ml.). The organic phase is washed with 10% sodium hydroxide and saturated salt solution, and dried over magnesium sulfate. After evaporation of the solvent, the product is crystallized from hexane to give 42.3 g. of cyclohexyl (2,3-dichloro-4-methoxyphenyl) ketone, which melts at 97—98°C.

Elemental analysis for $C_{14}H_{16}Cl_2O_2$:

Calc.: C, 58.55; H, 5.62;

Found: C, 58.92; H, 5.64.

Step B: 1-Bromocyclohexyl(2,3-dichloro-4-methoxyphenyl) ketone

Bromine (22.4 g., 0.14 mole) in acetic acid (50 ml.) is added dropwise to a stirred solution of cyclohexyl(2,3-dichloro-4-methoxyphenyl) ketone (40 g., 0.14 mole) and 30% hydrobromic acid (0.5 ml.) in acetic acid (400 ml.) during a one and a half hours at 25°C. The mixture is poured into water (1 l.) and sodium bisulfite (10 g.). The product that precipitates is crystallized from cyclohexane to give 47.3 g. of 1-bromocyclohexyl(2,3-dichloro-4-methoxyphenyl) ketone, which melts at 94—95°C.

Elemental analysis for $C_{14}H_{15}BrCl_2O_2$:

Calc.: C, 45.93; H, 4.13;

Found: C, 45.77; H, 4.11.

Step C: 1-Cyclohexenyl(2,3-dichloro-4-methoxyphenyl) ketone

1-Bromocyclohexyl (2,3-dichloro-4-methoxyphenyl) ketone (47.3 g., 0.13 mole), lithium chloride (16.5 g., 0.39 mole) and dimethylformamide (200 ml.) are heated at 90°C. for two hours, then poured into water (1 l.) to give 36.5 g. of 1-cyclohexenyl (2,3-dichloro-4-methoxyphenyl) ketone, which melts at 126—129°C. after drying at 60°C. under vacuum for 16 hours.

Elemental analysis for $C_{14}H_{14}Cl_2O_2$:

Calc.: C, 58.96; H, 4.95;

Found: C, 58.87; H, 5.10.

Step D: 1 α ,1,2,3,4,4 α -Hexahydro-6-methoxy-7,8-dichlorofluoren-9-one

A stirred mixture of 1-cyclohexenyl (2,3-dichloro-4-methoxyphenyl) ketone (34 g., 0.12 mole) and polyphosphoric acid (340 g.) is heated at 90°C. for 17 hours in a resin pot. Crushed ice (1 kg.) is added to precipitate the product which, on crystallization from benzene:cyclohexane, 1:1, gives 18.4 g. of 1 α ,1,2,3,4,4 α -hexahydro-6-methoxy-7,8-dichlorofluoren-9-one, which melts at 169—171°C.

Elemental analysis for $C_{14}H_{14}Cl_2O_2$:

Calc.: C, 58.96; H, 4.95;

Found: C, 59.35; H, 5.43.

Step E: 1 α -phenyl-1 α ,1,2,3,4,4 α -hexahydro-6-methoxy-7,8-dichlorofluoren-9-one

Potassium *tert*-butoxide (1.69 g., 0.015 mole) in *tert*-butanol (40 ml.) is added to a refluxing solution of 1 α ,1,2,3,4,4 α -hexahydro-6-methoxy-7,8-dichlorofluoren-9-one (2.85 g., 0.01 mole) in dry benzene (50 ml.) and *tert*-butanol (10 ml.) under nitrogen, and refluxing is continued for 0.5 hour. The reaction mixture is cooled to 25°C., diphenyliodonium chloride (4.75 g., 0.015 mole) is added and refluxing is continued for 2 hours. The reaction mixture is cooled to 25°C., 50 ml. water is added, and the mixture is concentrated to dryness *in vacuo* to give 3.0 g. of 1 α -

phenyl-1 α ,1,2,3,4,4 α -hexahydro-6-methoxy-7,8-dichlorofluoren-9-one, which melts at 136—142°C. and is used without further purification.

Step F: 1 α -Phenyl-1 α ,1,2,3,4,4 α -hexahydro-6-hydroxy-7,8-dichlorofluoren-9-one
A stirred mixture of 1 α -phenyl-1 α ,1,2,3,4,4 α -hexahydro-6-methoxy-7,8-dichlorofluoren-9-one (3.0 g., 0.0083 mole) and pyridine hydrochloride (30 g.) is heated at 180°C. for 2 hours, then poured into water (800 ml.). The 1 α -phenyl-1 α ,1,2,3,4,4 α -hexahydro-6-hydroxy-7,8-dichlorofluoren-9-one, which separates (1.71 g.), melts at 213—215°C. after crystallization from absolute ethanol.

Elemental analysis for $C_{15}H_{16}Cl_2O_2$:
Calc.: C, 65.72; H, 4.64;
Found: C, 66.27; H, 4.78.

Step G: (1,2-Dichloro-5 α ,5,6,7,8 α -hexahydro-8 α -phenyl-9-oxo-fluoren-3-yloxy)acetic acid

A stirred mixture of 1 α -phenyl-1 α ,1,2,3,4,4 α -hexahydro-6-hydroxy-7,8-dichlorofluoren-9-one (1.7 g., 0.0049 mole), potassium carbonate (1.36 g., 0.0098 mole) and ethyl bromoacetate (1.64 g., 0.0098 mole) in dimethylformamide (50 ml.) is warmed at 55—60°C. for 3 hours, then treated with water (50 ml.) and 10N sodium hydroxide solution (2.5 ml., 0.025 mole) and heated at 80°C. for 1.5 hours. The reaction mixture is added slowly to water (500 ml.) and 12N hydrochloric acid (10 ml.) to precipitate 1.51 g. of (1,2-dichloro-5 α ,5,6,7,8 α -hexahydro-8 α -phenyl-9-oxo-fluoren-3-yloxy)acetic acid, which melts at 194—196°C. after crystallization from acetic acid:water, 1:1.

Elemental analysis for $C_{21}H_{18}Cl_2O_4$:
Calc.: C, 62.24; H, 4.48;
Found: C, 62.27; H, 4.56.

EXAMPLE 27.

Preparation of (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid

Step A: *Tert*-butyl(1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetate
A mixture of 2-methyl-2-phenyl-5-hydroxy-6,7-dichloro-1-indanone (9.2 g., 0.03 mole), potassium carbonate (8.29 g., 0.06 mole) and *tert*-butyl bromoacetate (6.44 g., 0.033 mole) in dimethylformamide (30 ml.) is stirred at 25°C. for two hours. The reaction mixture is poured into cold water (150 ml.) and the *tert*-butyl (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetate, which separates, is filtered, rinsed with water and dried.

Step B: (1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid
A solution of *tert*-butyl (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetate (1.0 g., 0.00237 mole) in benzene (25 ml.) is treated with methanesulfonic acid (2 drops) and refluxed for half an hour. The reaction mixture is treated with cyclohexane (20 ml.) and cooled, affording (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid, which is filtered and dried.

EXAMPLE 28.

Preparation of [1-Oxo-2-methyl-2-(2-thienyl)-6,7-dichloro-5-indanyloxy]acetic acid

Step A: 2,2'-Dithienyl iodonium chloride
To acetic anhydride (70 ml.) at -20°C. there is added dropwise with stirring fuming nitric acid (27 ml.), then iodine (25 g., 0.1 mole) and trifluoroacetic acid (47 ml., 0.61 mole). The mixture is left to warm to ambient temperature while the iodine dissolves over 3 hours. The solvent is removed by distillation *in vacuo*, the pot temperature never exceeding 50°C. The residue is dissolved in acetic anhydride (150 ml.), the solution cooled to -10°C. and a mixture of thiophene (63 ml., 0.08 mole), acetic anhydride (350 ml.) and trifluoroacetic acid (50 ml.) is added dropwise over one hour. After cooling at 5°C. for 17 hours, the mixture is distilled *in vacuo*, the pot temperature never exceeding 50°C. Water (500 ml.) is added to the residue, the solution is filtered and ammonium chloride (21.36 g., 0.4 mole) in water (100 ml.) is added to precipitate 26.6 g. of 2,2'-dithienyl iodonium chloride, which melts at 235—236°C. after crystallization from methanol.

which

ren-9-one
fro - 6 -
ne hyd-
(800 ml.),
ren-9-one,
absolute

1-3-yloxy).

cy-7,8-di-
0.0098
(50 ml.)
and 10N
5 hours.
oric acid
-phenyl-
crystal-

tate
(9.2 g.,
acetate
or two
-butyl
tes, is

loxy)-
lionic
with
chloro-

rring
d (47
the
the
ctic
(63
) is
e is
) is
0.4
ium

Elemental analysis for $C_8H_6ClIS_2$:

Calc.: C, 28.24; H, 1.84;

Found: C, 28.90; H, 1.92.

Step B: 2-Methyl-2-(2-thienyl)-5-methoxy-6,7-dichloro-1-indanone

Potassium *tert*-butoxide (5.06 g., 0.045 mole) dissolved in *tert*-butanol (100 ml.) is added to a refluxing solution of 2-methyl-5-methoxy-6,7-dichloro-1-indanone prepared by the method described in Example 5, Steps A to D, (7.35 g., 0.03 mole) in *tert*-butanol (150 ml.) and benzene (150 ml.), refluxing is continued for 3 hours under nitrogen, then the mixture is cooled slightly and solid dithienyliodonium chloride (16.5 g., 0.05 mole) is added in one portion. Heating at reflux is continued for 2 hours. The reaction mixture is cooled to 25°C., 100 ml. water added, and the mixture concentrated to dryness *in vacuo* to give 3.85 g. of 2-methyl-2-(2-thienyl)-5-methoxy-6,7-dichloro-1-indanone, which melts at 145–146.5°C. after trituration with ether and crystallization from benzene:hexane, 1:4.

Elemental analysis for $C_{11}H_{12}Cl_2O_2S$:

Calc.: C, 55.06; H, 3.70;

Found: C, 55.24; H, 3.77.

Step C: 2-Methyl-2-(2-thienyl)-5-hydroxy-6,7-dichloro-1-indanone

A stirred mixture of 2-methyl-2-(2-thienyl)-5-methoxy-6,7-dichloro-1-indanone (3.65 g., 0.0112 mole) and pyridine hydrochloride (36 g.) is heated at 175°C. for half an hour, then poured into crushed ice-water (500 ml.). The 2-methyl-2-(2-thienyl)-5-hydroxy-6,7-dichloro-1-indanone, which separates (3.37 g.), melts at 224–226°C. after crystallization from ethanol:water, 2:1.

Elemental analysis for $C_{11}H_{10}Cl_2O_2S$:

Calc.: C, 53.69; H, 3.22;

Found: C, 53.27; H, 3.36.

Step D: [1-Oxo-2-methyl-2-(2-thienyl)-6,7-dichloro-5-indanyloxy]acetic acid

A stirred mixture of 2-methyl-2-(2-thienyl)-5-hydroxy-6,7-dichloro-1-indanone (3.13 g., 0.01 mole), potassium carbonate (2.77 g., 0.02 mole) and ethyl bromoacetate (3.34 g., 0.02 mole) in dimethylformamide (40 ml.) is warmed at 55–60°C. for 2 hours, then treated with water (40 ml.) and 10N sodium hydroxide solution (4 ml., 0.04 mole), and heated at 100°C. for one hour. The reaction mixture is added slowly to crushed ice-water (700 ml.) and 12N hydrochloric acid (10 ml.) to precipitate 1.78 g. of [1-oxo-2-methyl-2-(2-thienyl)-6,7-dichloro-5-indanyloxy]acetic acid, which melts at 161–162°C. after crystallization from nitromethane.

Elemental analysis for $C_{16}H_{12}Cl_2O_4S$:

Calc.: C, 51.78; H, 3.24; Cl, 19.10;

Found: C, 51.66; H, 3.34; Cl, 19.21.

EXAMPLE 29.

Where in Example 5, Step A, there is substituted for the 2,3-dichloroanisole an equivalent amount of 2-chloro-3-methylanisole, 2,3-dimethylanisole, 3-methylanisole, or 2-methyl-3-chloroanisole, respectively, and Steps B to D in Example 5 and Steps A to D in Example 28 are carried out as described, there is obtained:

[1-oxo-2-(2-thienyl)-2,7-dimethyl-6-chloro-5-indanyloxy]acetic acid;

[1-oxo-2-(2-thienyl)-2,6,7-trimethyl-5-indanyloxy]acetic acid;

[1-oxo-2-(2-thienyl)-2,7-dimethyl-5-indanyloxy]acetic acid; or

[1-oxo-2-(2-thienyl)-2,6-dimethyl-7-chloro-5-indanyloxy]acetic acid.

EXAMPLE 30.

Where in Example 28, Step A, there is substituted for the thiophene an equivalent amount of 2-methylthiophene, 2-bromothiophene, 2-chlorothiophene, or 2,5-dimethylthiophene, respectively, and Steps B to D are employed as described, there is obtained:

[1-oxo-2-methyl-2-(5-methyl-2-thienyl)-6,7-dichloro-5-indanyloxy]acetic acid;
 [1-oxo-2-methyl-2-(5-bromo-2-thienyl)-6,7-dichloro-5-indanyloxy]acetic acid;
 [1-oxo-2-methyl-2-(5-chloro-2-thienyl)-6,7-dichloro-5-indanyloxy]acetic acid;
 or

5 [1-oxo-2-methyl-2-(2,5-dimethyl-3-thienyl)-6,7-dichloro-5-indanyloxy]acetic acid.

EXAMPLE 31.

Preparation of [1-Oxo-2-(4-aminomethylphenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid

10 Step A: [1-Oxo-2-[4-(2-chloroacetamidomethyl)phenyl]-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid

Well-pulverized N-hydroxymethyl-2-chloroacetamide (3.37 g., 0.0274 mole) is added portionwise to (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid (10.0 g., 0.0274 mole) in 36N sulfuric acid (100 ml.) and acetic acid (100 ml.) with stirring at 40–50°C. over half an hour. Additional N-hydroxymethyl-2-chloroacetamide (1.68 g., 0.014 mole) is added over a four-hour period until no starting material remains. After stirring at 25°C. for 16 hours, the reaction mixture is added to crushed ice-water (2 l.) to precipitate 11.9 g. of [1-oxo-2-[4-(2-chloroacetamidomethyl)phenyl]-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid, which melts at 138–141°C. and is used in the next step without purification.

20 Step B: Ethyl[1-oxo-2-(4-aminomethylphenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetate hydrochloride

[1 - Oxo - 2 - [4 - (2 - chloroacetamidomethyl)phenyl] - 2 - methyl - 6,7 - dichloro-5-indanyloxy]acetic acid (2.0 g., 0.004 mole), absolute ethanol (20 ml.) and 12N hydrochloric acid (7 ml.) are combined and heated at reflux for 3 hours. On cooling to 5°C. 1.14 g. of ethyl [1-oxo-2-(4-aminomethylphenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetate hydrochloride is precipitated, it melts at 211–213°C. after crystallization from ethanol.

30 Elemental analysis for $C_{21}H_{21}Cl_2NO_4 \cdot HCl$:

Calc.: C, 54.98; H, 4.83; N, 3.05;

Found: C, 54.39; H, 4.72; N, 2.76.

Step C: [1-oxo-2-(4-aminomethylphenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid sodium salt

35 Ethyl [1-oxo-2-(4-aminomethylphenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetate hydrochloride (1.57 g., 0.0034 mole), sodium bicarbonate (1.15 g., 0.0136 mole), absolute ethanol (50 ml) and water (50 ml) are combined and heated at reflux for 1.5 hours leaving a solution which is filtered and then neutralized with 1N hydrochloric acid (10.26 ml., 0.01026 mole) to precipitate 900 mg of [1-oxo-2-(4-aminomethylphenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid sodium salt, which melts at 270–271°C. after drying.

40 Elemental analysis for $C_{19}H_{17}Cl_2NO_4Na$:

Calc.: C, 54.83; H, 3.87; N, 3.37;

Found: C, 55.07; H, 4.27; N, 3.20.

45 The sodium salt of (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid may be obtained from the product of Example 1 by a similar procedure.

EXAMPLE 32.

Resolution of the Optical Isomers of (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid

50 Step A: (+)-isomer

A mixture of racemic (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid (26 g., 0.071 mole) and L-(–)- α -methylbenzylamine (8.6 g., 0.071 mole) is dissolved in hot acetonitrile (250 ml) and aged at 25°C for 18 hours.

55 The acetonitrile is decanted from the resultant salt (13.2 g.), which is recrystallized three times from a minimum volume of 2-propanol, thus affording 1.9 g. of the salt of the pure (+) enantiomer. This is converted to the acid by

cetic acid;

cetic acid;

cetic acid;

ylacetic

pro-5-

hloro-5-

mole) is
xy)acetic
(100 ml.)
nethyl-2-
until no
mixture
2-chloro-
l, which

anyloxy]-

1 - 6,7 -
(20 ml.)
3 hours.
methyl-
t 211—

lacetic

xyloxy]-
mole),
for 1.5
chloric
nethyl-
elts at

loxy)-
pro-

o-5-

oxy)-
0.071
rs.
h is
ding
d by

treatment of the salt with dilute hydrochloric acid and ether. The ethereal phase is washed with water and dried over magnesium sulfate and the ether is distilled off at reduced pressure. The (+)-isomer melts at 163°C after crystallization from toluene.

$$[\alpha]_D^{25} = +88^\circ \text{C. (C, 2, acetone)}$$

Step B: (-)-isomer

By following substantially the procedure described in Step A using as the reactants partially resolved (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)-acetic acid (15.5 g., 0.042 mole), obtained from the acetonitrile mother liquor of Step A, and D-(+)-methylbenzylamine (5.15 g., 0.042 mole) in acetonitrile (150 ml) and recrystallizing the resultant salt three times from a minimum volume of 2-propanol, there is obtained 2.2 g of the salt of the pure (-)-enantiomer. The (-)-isomer melts at 164°C after crystallization from toluene.

$$[\alpha]_D^{25} = -88^\circ \text{C. (C, 2, acetone)}$$

The compounds of this invention can be administered in a wide variety of therapeutic dosages in conventional vehicles. The present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I and a pharmaceutically acceptable carrier. For example, the compounds can be administered orally in the form of a tablet or by intravenous injection. The daily dosage of the products may be varied over a wide range, for example, in the form of scored tablets containing 2.5, 1, 5, 10, 25, 50, 100, 150, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. These dosages are well below the toxic or lethal dose of the products.

A suitable unit dosage form of the products of this invention can be administered by mixing 50 milligrams of a [1-oxo-2-aryl or 2-thienyl-2-substituted-5-indanyloxy (or thio)lalkanoic acid (I) of this invention or a suitable salt, ester, amide or 5-tetrazolyl analogue thereof, with 149 mg. of lactose and 1 mg. of magnesium stearate and placing the mixture into a No. 1 gelatin capsule. Similarly, by using more of the active ingredient and less lactose, other dosage forms can be put up in No. 1 gelatin capsules. Should it be necessary compressed tablets, pills, or other desired unit dosages can be prepared to incorporate the compounds of this invention by conventional methods, and, if desired, can be made up as elixirs or as injectable solutions by methods well known to pharmacists. An effective amount of the drug is ordinarily supplied at a dosage level of from 0.025 mg. to 20 mg./kg., preferably 0.06 mg. to 7 mg./kg., of body weight.

It is also within the scope of this invention to combine two or more of the compounds of this invention in a unit dosage form or to combine one or more of the compounds of this invention with other known diuretics and saluretics or with other desired therapeutic and/or nutritive agents in dosage unit form. For example, the compounds of this invention can be combined with anti-hypertensive compounds, and particularly with an agent such as methyl-dopa or reserpine. Also a combination or mixture of different indanones of Formula I with each other can be advantageous particularly where one compound has greater diuretic activity and the other has greater uricosuric activity.

The following examples illustrate the preparation of representative dosage forms.

EXAMPLE 33.

Preparation of dry-filled capsules containing 10 mg. of active ingredient per capsule

	Per Capsule
(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid	10 mg.
Lactose	189 mg.
Magnesium stearate	1 mg.
Capsule (Size No. 1)	200 mg.

The (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid is reduced to a No. 60 powder and then lactose and magnesium stearate are passed through a No. 60 bolting cloth onto the powder and the combined ingredients mixed for 10 minutes and then filled into a No. 1 dry gelatin capsule.

Similar dry-filled capsules can be prepared by replacing the active ingredient of the above example by a molar equivalent amount of any of the other novel compounds of this invention.

EXAMPLE 34.

Parenteral Solution of Sodium (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetate

(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid (1 gm.) is treated with sodium bicarbonate (0.25 gm.) in water (10 ml.) and the mixture stirred and heated to effect solution. The solution is diluted with water to a volume of 50 ml. and sterilized by autoclaving at 120°C. for one hour.

EXAMPLE 35.

Dry-filled capsules containing 10 mg. of active ingredient and 0.125 mg. of reserpine per capsule

	Per Capsule
(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid	10 mg.
Reserpine	0.125 mg.
Lactose	188.875 mg.
Magnesium stearate.	1 mg.
Capsule (Size No. 1)	200 mg.

The (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid and reserpine are united and reduced to a No. 60 powder and then lactose and magnesium stearate are passed through a No. 60 bolting cloth onto the powder and the combined ingredients are admixed for ten minutes and then filled into a No. 1 dry gelatin capsule.

Similar dry-filled capsules can be prepared by replacing the indanyloxyacetic acid ingredient of the above example by any of the compounds of this invention.

EXAMPLE 36.

Dry-filled capsules containing 10 mg. of active ingredient and 250 mg. of levo-3-(3,4-dihydroxyphenyl)-2-methylalanine

	Per Capsule
(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid	10 mg.
Levo-3-(3,4-dihydroxyphenyl)-2-methylalanine	265 mg.
Lactose	124 mg.
Magnesium stearate	1 mg.
Capsule (Size No. 0)	400 mg.

The (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid and levo-3-(3,4-dihydroxyphenyl)-2-alanine are united and reduced to a No. 60 powder and then lactose and magnesium stearate are passed through a No. 60 bolting cloth

acid is
are passed
ingredients

ingredient
ther no

pro-5-

1 gm.) is
mixture
a volume

mg. of

nd re-
e and
er and
No. 1

acetic
ition.

of

nd
er
th

onto the powder and the combined ingredients admixed for ten minutes and then filled into a No. 0 dry gelatin capsule.

EXAMPLE 37.

Dry-filled capsules containing 50 mg. of active ingredient per capsule

	5		Per Capsule	5
		(1-Oxo-2-methyl-2-(2-thienyl)-6,7-dichloro-5-indanyloxy)acetic acid	50 mg.	
		Lactose	149 mg.	
		Magnesium Stearate	1 mg.	
		Capsule (Size No. 1)	200 mg.	10

The (1-oxo-2-methyl-2-(2-thienyl)-6,7-dichloro-5-indanyloxy)acetic acid is reduced to a No. 60 powder and then lactose and magnesium stearate are passed through a No. 60 bolting cloth onto the powder and the combined ingredients admixed for 10 minutes and then filled into a No. 1 dry gelatin capsule.

Similar dry-filled capsules can be prepared by replacing the active ingredient of the above example by a molar equivalent amount of any of the other novel compounds of this invention.

EXAMPLE 38.

Parenteral Solution of sodium(1-oxo-2-methyl-2-(2-thienyl)-6,7-dichloro-5-indanyloxy)acetate

(1-Oxo-2-methyl-2-thienyl-6,7-dichloro-5-indanyloxy)acetic acid (1 gm.) is treated with sodium bicarbonate (0.25 gm.) in water (10 ml.) and the mixture stirred and heated to effect solution. The solution is diluted with water to a volume of 50 ml. and sterilized by autoclaving at 120°C. for one hour.

EXAMPLE 39.

Dry-filled capsules containing 25 mg. of active ingredient and 0.125 mg. of reserpine per capsule

			Per Capsule	
	30	(1-Oxo-2-methyl-2-(2-thienyl)-6,7-dichloro-5-indanyloxy)acetic acid	25 mg.	30
		Reserpine	0.125 mg.	
		Lactose	173.875 mg.	
		Magnesium stearate	1 mg.	
		Capsule (Size No. 1)	200 mg.	

The (1-oxo-2-methyl-2-(2-thienyl)-6,7-dichloro-5-indanyloxy)acetic acid and reserpine are united and reduced to a No. 60 powder and then lactose and magnesium stearate are passed through a No. 60 bolting cloth onto the powder and the combined ingredients are admixed for ten minutes and then filled into a No. 1 dry gelatin capsule.

Similar dry-filled capsules can be prepared by replacing the indanyloxyacetic acid ingredient of the above example by any of the compounds of this invention.

EXAMPLE 40.

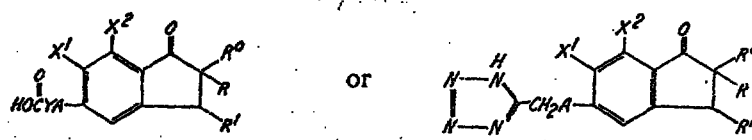
Dry-filled capsules containing 10 mg. of active ingredient and 250 mg. of levo-3-(3,4-dihydroxyphenyl)-2-methylalanine

		Per Capsule	
5	(1-Oxo-2-methyl-2-(2-thienyl)-6,7-dichloro-5-indanyloxy)acetic acid	10 mg.	5
	Levo-3-(3,4-dihydroxyphenyl)-2-methylalanine	250 mg.	
	Lactose	139 mg.	
10	Magnesium stearate	1 mg.	10
	Capsule (Size No. 0)	400 mg.	

15 The (1-oxo-2-methyl-2-(2-thienyl)-6,7-dichloro-5-indanyloxy)acetic acid and levo-3-(3,4-dihydroxyphenyl)-2-alanine are united and reduced to a No. 60 powder and then lactose and magnesium stearate are passed through a No. 60 bolting cloth onto the powder and the combined ingredients admixed for ten minutes and then filled into a No. 0 dry gelatin capsule.

WHAT WE CLAIM IS:—

1. A compound of the formula:



20 in which R⁰ is

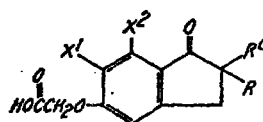


or



25 A is oxygen or sulphur; R is C₁₋₃ alkyl, C₃₋₅ alkenyl, phenyl-(C₁₋₃ alkyl), phenyl-(C₃₋₅ alkenyl), aryl, substituted aryl, cycloalkyl or cycloalkyl-(C₁₋₃ alkyl); R¹ is hydrogen, C₁₋₃ alkyl or aryl; or R¹ and R are joined together to form a C₁₋₄ bivalent hydrocarbon chain; Y is alkylene or haloalkylene containing from 1 to 4 carbon atoms; X³ is hydrogen, nitro, hydroxy, C₁₋₃ alkyl, C₁₋₃ alkoxy, cycloalkyl, halo, amino, cyano, sulfamoyl, methanesulfonyl, chlorosulfonyl, aminomethyl, acylamino or acylaminomethyl; X⁴ is hydrogen, C₁₋₃ alkyl, aminomethyl or halogen; X⁵ is hydrogen or C₁₋₃ alkyl and X⁶ is hydrogen, halogen or methyl and X⁷ is halogen, methyl or trihalomethyl; or X⁵ and X⁶ are joined together to form a bivalent hydrocarbon chain containing 3 or 4 carbon atoms; and the non-toxic, pharmacologically acceptable salts, amides, anhydrides and esters thereof.

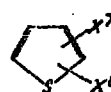
30 2. A compound of the formula:



35 in which R⁰ is



or



35

EXAMPLE 40.

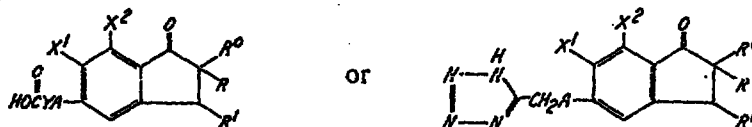
Dry-filled capsules containing 10 mg. of active ingredient and 250 mg. of levo-3-(3,4-dihydroxyphenyl)-2-methylalanine

		Per Capsule	
5	(1-Oxo-2-methyl-2-(2-thienyl)-6,7-dichloro-5-indanyloxy)acetic acid	10 mg.	5
	Levo-3-(3,4-dihydroxyphenyl)-2-methylalanine	250 mg.	
	Lactose	139 mg.	
10	Magnesium stearate	1 mg.	10
	Capsule (Size No. 0)	400 mg.	

The (1-oxo-2-methyl-2-(2-thienyl)-6,7-dichloro-5-indanyloxy)acetic acid and levo-3-(3,4-dihydroxyphenyl)-2-alanine are united and reduced to a No. 60 powder and then lactose and magnesium stearate are passed through a No. 60 bolting cloth onto the powder and the combined ingredients admixed for ten minutes and then filled into a No. 0 dry gelatin capsule.

WHAT WE CLAIM IS:—

1. A compound of the formula:



20 in which R⁰ is



or



20

A is oxygen or sulphur; R is C₁₋₃ alkyl, C₃₋₅ alkenyl, phenyl-(C₁₋₃ alkyl), phenyl-(C₁₋₃ alkenyl), aryl, substituted aryl, cycloalkyl or cycloalkyl-(C₁₋₃ alkyl); R¹ is hydrogen, C₁₋₃ alkyl or aryl; or R¹ and R are joined together to form a C₁₋₄ bivalent hydrocarbon chain; Y is alkylene or haloalkylene containing from 1 to 4 carbon atoms; X³ is hydrogen, nitro, hydroxy, C₁₋₃ alkyl, C₁₋₃ alkoxy, cycloalkyl, halo, amino, cyano, sulfamoyl, methanesulfonyl, chlorosulfonyl, aminomethyl, acylamino or acylaminomethyl; X⁷ is hydrogen, C₁₋₃ alkyl, aminomethyl or halogen; X⁸ is hydrogen or C₁₋₃ alkyl and X¹ is hydrogen, halogen or methyl and X² is halogen, methyl or trihalomethyl; or X¹ and X² are joined together to form a bivalent hydrocarbon chain containing 3 or 4 carbon atoms; and the non-toxic, pharmacologically acceptable salts, amides, anhydrides and esters thereof.

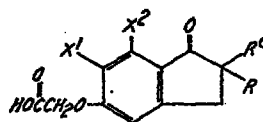
25

25

30

30

2. A compound of the formula:



35 in which R⁰ is



or



35



R is C_{1-5} alkyl; each of X^1 and X^2 , which are similar or dissimilar, is chlorine or methyl; X^3 is hydrogen, nitro, hydroxy, C_{1-5} alkyl, C_{1-5} alkoxy, cycloalkyl, halo, amino, cyano, sulfamoyl, methanesulfonyl, chlorosulfonyl or aminomethyl; X^7 is hydrogen, C_{1-5} alkyl, halogen or aminomethyl; and X^8 is hydrogen or C_{1-5} alkyl; and the non-toxic, pharmacologically acceptable salts thereof.

3. A compound according to Claim 2 in which X^3 is hydrogen, methyl, chlorine, fluorine, hydroxy, amino or aminomethyl; X^7 is hydrogen; and X^8 is hydrogen.

4. (1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid.

5. (-) (1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid.

6. (+) (1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid.

7. The sodium salt of the compound according to Claim 4.

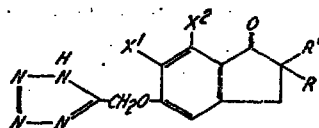
8. [1-Oxo-2-(4-chlorophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid.

9. [1-Oxo-2-(4-fluorophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid.

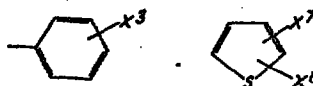
10. [1-Oxo-2-(2-thienyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid.

11. [1-Oxo-2-(4-aminophenyl)-2-methyl-6,7-dichloro-5-indanyloxy]acetic acid.

12. A compound of the formula:

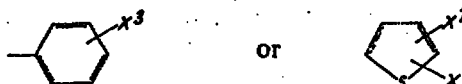


where R^0 is



R is C_{1-5} alkyl; each of X^1 and X^2 is methyl or chloro; X^3 is hydrogen, nitro, hydroxy, C_{1-5} alkyl, C_{1-5} alkoxy, cycloalkyl, halo, amino, cyano, sulfamoyl, methanesulfonyl, chlorosulfonyl or aminomethyl; X^7 is hydrogen, C_{1-5} alkyl or halogen; and X^8 is hydrogen or C_{1-5} alkyl; or a pharmacologically acceptable salt thereof.

13. A compound according to Claim 12 in which R^0 is



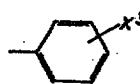
X^3 is hydrogen, methyl, chlorine or fluorine; and X^7 and X^8 are hydrogen.

14. 5-(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxymethyl)tetrazole.

15. A pharmaceutical composition comprising a therapeutically effective amount of a compound as claimed in Claim 1 and a pharmaceutically acceptable carrier.

16. A composition as claimed in Claim 15, in which the said compound is a compound as claimed in Claim 2.

17. A composition as claimed in Claim 15, in which, in the formulae R^0 is



X^3 is hydrogen, methyl, chlorine or fluorine; X^7 is hydrogen and X^8 is hydrogen.

18. A composition as claimed in Claim 16 in which the compound is (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid.

19. A composition as claimed in Claim 16, in which the compound is a compound as claimed in any one of Claims 3 and 5-14.

20. A composition as claimed in any one of Claims 16-19, in orally administrable form.

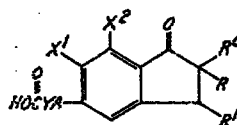
21. A composition as claimed in any one of Claims 16-19, in parenterally injectable form.

22. A composition as claimed in Claim 20, in the form of a tablet or capsule.



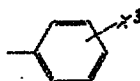
23. A composition as claimed in any one of Claims 16—22, that also contains a second pharmaceutically active compound.

24. A process for preparing a compound of the formula:

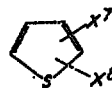


5

in which R⁰ is

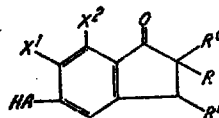


or



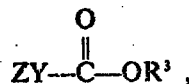
5

where X³ is hydrogen, nitro, C₁₋₅ alkyl, C₁₋₅ alkoxy, cycloalkyl, halo, amino, cyano, sulfamoyl, or methanesulfonyl; and A, R, R¹, Y, X¹, X², X⁷, and X⁸ are as defined in Claim 1, that comprises treating a compound of the formula:



10

in which A, R⁰, R, R¹, X¹, X², X³, X⁷ and X⁸ are as defined above with a reagent of the formula:



10

where Y is as defined above, Z is halogen and R³ is hydrogen or C₁₋₅ alkyl, in the presence of a base and, when R³ is C₁₋₅ alkyl, hydrolysing the resulting ester, to produce the desired product.

15

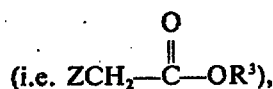
25. A process as claimed in Claim 24, in which, in the formulae, Y is methylene, A is oxygen, and R, X¹, X² and X⁸ are as defined in Claim 2, X³ is hydrogen, nitro, C₁₋₅ alkyl, C₁₋₅ alkoxy, cycloalkyl, halo, amino, cyano, sulfamoyl, methanesulfonyl; and X⁷ is hydrogen, C₁₋₅ alkyl or halogen.

15

20

26. A modification of the process claimed in Claim 24 and 25 in which, in the second formula

20



Z is halo and R³ is *t*-butyl and the *t*-butyl ester produced in the first step is pyrolysed to form the desired product.

25

27. A process as claimed in Claim 25 in which R⁰ is

25



or



X³ is hydrogen, methyl, chlorine or fluorine; R is C₁₋₅ alkyl; and each of X¹ and X² is methyl or chlorine.

30

28. A process as claimed in Claim 27 in which the starting materials are chosen so that the product is (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)-acetic acid, and the base used is potassium carbonate.

30

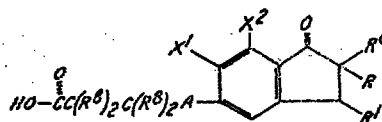
29. A process as claimed in Claim 26 in which the starting materials are chosen so that the product is (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)-acetic acid, and the base used is potassium carbonate.

35

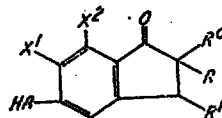
30. A process for preparing a compound of the formula:

35

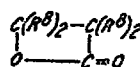




in which A, R, R¹, X¹ and X² are as defined in Claim 1, and R⁰ is as defined in Claim 24 and each R⁸ is hydrogen, methyl or ethyl, the four R⁸'s together containing 0, 1 or 2 carbon atoms, that comprises treating a compound of the formula:

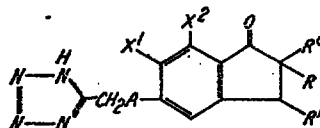


with a compound of the formula:

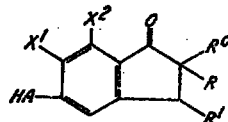


in the presence of a base, and acidifying the resulting ester to obtain the desired compound.

31. A process for preparing a compound of the formula:



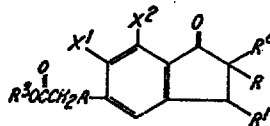
in which A, R, R¹, X¹ and X² are as defined in Claim 1 and R⁰ is as defined in Claim 24 that comprises treating a compound of the formula:



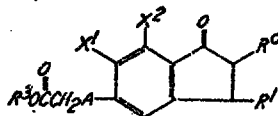
with a haloacetonitrile in the presence of a base and treating the resulting intermediate nitrile with sodium azide and ammonium chloride to produce the desired product.

32. A process according to Claim 31 that comprises reacting 2-methyl-2-phenyl-5-hydroxy-6,7-dichloro-1-indanone with chloroacetonitrile in the presence of potassium carbonate and treating the intermediate nitrile with sodium azide and ammonium chloride to produce 5-(1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxymethyl)tetrazole.

33. A process for preparing a compound of the formula:

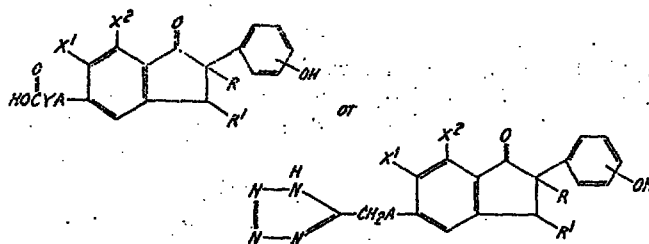


that comprises treating a compound of the formula:

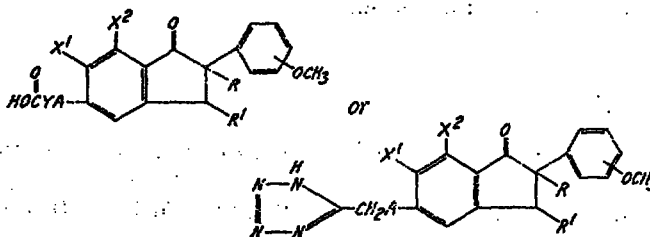


with an alkylating agent of the formula RZ, where R⁰, R¹ and Z are as defined in Claim 24 and A, R, R¹, X¹ and X² are as defined in Claim 1.

34. A process for preparing a compound of the formula:

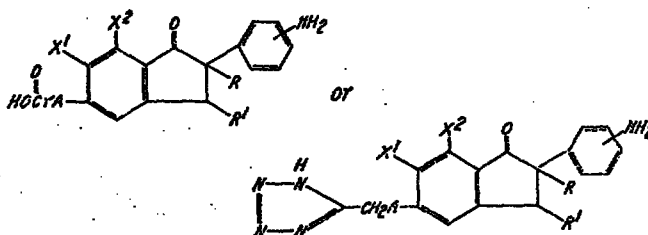


5 in which A, R, R¹, Y, X¹ and X² are as defined in Claim 1, that comprises treating a compound of the formula:

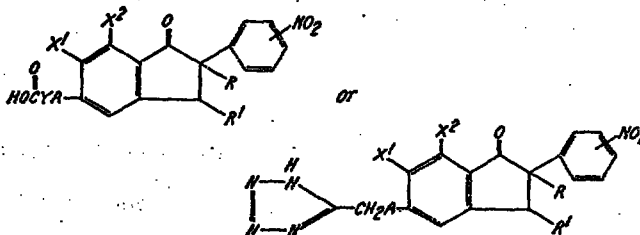


with an ether-cleaving reagent.

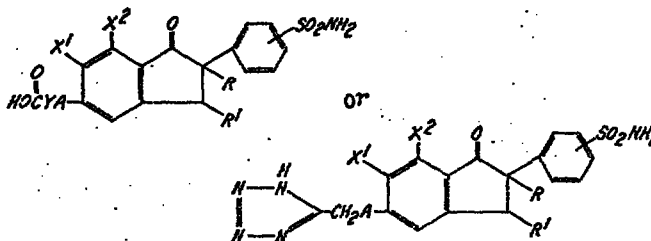
35. A process for preparing a compound of the formula:



in which A, R, R¹, Y, X¹ and X² are as defined in Claim 1, that comprises reducing a compound of the formula:



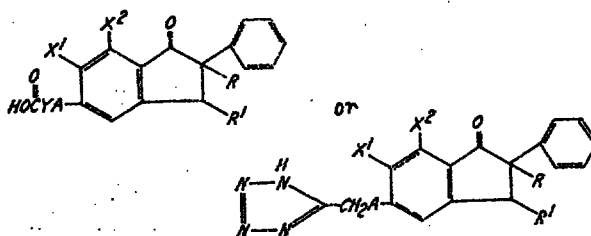
36. A process for preparing a compound of the formula:



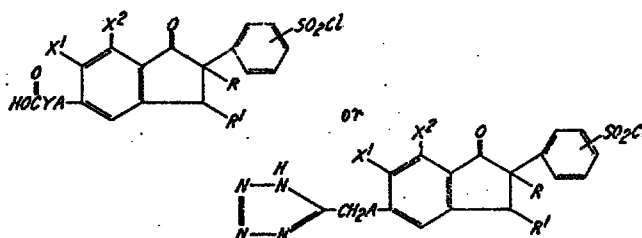
in which
A is oxygen or sulphur;



R is C_{1-5} alkyl, C_{3-5} alkenyl, cycloalkyl or cycloalkyl- $(C_{1-5}$ alkyl); and
 R^1 is hydrogen, C_{1-5} alkyl or aryl, or
 R^1 and R are joined together to form a C_{1-4} alkylene radical; and
 X^1 is hydrogen, halogen or methyl; and
 X^2 is halogen, methyl or trihalomethyl, or
 X^1 and X^2 are joined together to form a C_{3-4} bivalent hydrocarbon chain;
 that comprises reacting a compound of the formula:

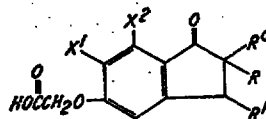


wherein X^1 , X^2 , A, Y, R and R^1 are as above defined with chlorosulfonic acid to form a compound of the formula:

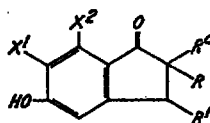


where A, R, R^1 , X^1 , X^2 and Y are as above defined and then reacting the latter compound with ammonia to form the desired product.

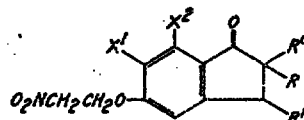
37. A process for preparing a compound of the formula:



in which R^0 is as defined in Claim 24 and R, R^1 , X^1 and X^2 are as defined in Claim 1, that comprises reacting a compound of the formula:



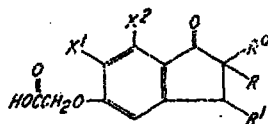
where X^1 , X^2 , R^0 , R and R^1 are as above defined with 1-halo-2-nitroethane to form a compound of the formula:



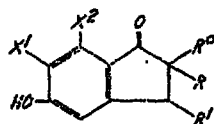
where X^1 , X^2 , R^0 , R and R^1 are as above and then hydrolysing the latter compound to form the desired product.

38. A process for preparing a compound of the formula:

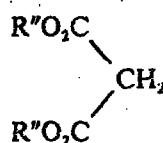




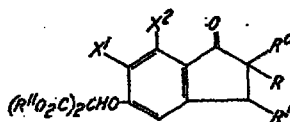
in which R^0 is as defined in Claim 24 and R , R^1 , X^1 and X^2 are as defined in Claim 1, that comprises reacting a compound of the formula:



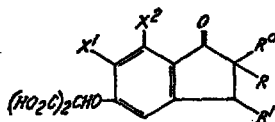
- 5 where X^1 , X^2 , R^0 , R and R^1 are as above defined with a malonic ester of the formula:



where R'' is C_{1-3} alkyl to form a compound of the formula:

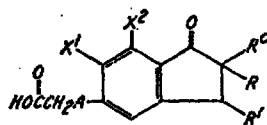


- 10 where X^1 , X^2 , R^0 , R , R^1 and R'' are as above defined; hydrolysing the latter compound to form a compound of the formula:

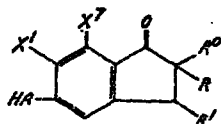


where X^1 , X^2 , R^0 , R , R^1 are as above defined and decarboxylating the latter compound to form the desired product.

- 15 39. A process for preparing a compound of the formula:



in which R^0 is as defined in Claim 24 and A , R , R^1 , X^1 and X^2 are as defined in claim 1, that comprises reacting a compound of the formula:



- 20 with a haloacetonitrile in the presence of a base followed by hydrolysis of the nitrile intermediate.



40. A pharmaceutical composition as claimed in claim 23, in which the second pharmaceutically active agent is an antihypertensive agent.

41. A pharmaceutical composition as claimed in claim 40 in which the antihypertensive agent is reserpine.

5 42. A pharmaceutical composition as claimed in claim 40 in which the antihypertensive agent is levo-3-(3,4-dihydroxyphenyl)-2-methylalanine. 5

43. A pharmaceutical composition as claimed in any one of claims 15—22, that comprises a therapeutically effective amount of two or more different compounds as claimed in any one of claims 1—14.

For the Applicants,
D. YOUNG & CO.,
Chartered Patent Agents,
9 and 10 Staple Inn,
London, WC1V 7RD.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1977.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.

