United States Patent Office 3,644,479 Patented Feb. 22, 1972

3,644,479

1-INDANCARBOXYLIC ACIDS AND DERIVATIVES

Peter Frederick Juby and Thomas William Hudyma, Dewitt, and Richard Anthony Partyka, Liverpool, N.Y., assignors to Bristol-Myers Company, New York, N.Y.

No Drawing. Filed Feb. 9, 1970, Ser. No. 9,963
Int. Cl. C07c 69/76
U.S. Cl. 260—469 5 Claims

ABSTRACT OF THE DISCLOSURE

5-phenyl-1-indancarboxylic acids are useful anti-inflammatory agents in the treatment of inflammatory diseases in animals, including man.

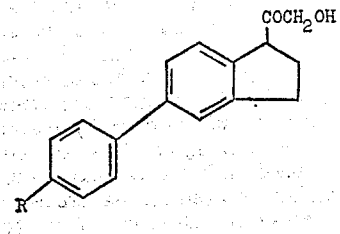
BACKGROUND OF THE INVENTION

(1) Field of the invention

The compounds of the present invention relate to 5-phenyl-1-indancarboxylic acids which compounds are useful non-steroidal anti-inflammatory agents.

(2) Description of the prior art

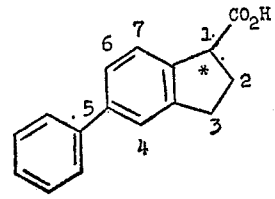
The compounds 4-isobutyl-phenylacetic acid [South African Pat. 62/294 (1962)], 4-isobutyl-α-methyl-phenylacetic acid [S. S. Adams, E. E. Cliffe, B. Lessel, and J. S. Nicholson, J. Pharm. Sci., 56, 1686 (1967)], 3-chloro-4-cyclohexyl-α-methylphenyl-acetic acid [T. Y. Shen, Chim. Therap., II 459 (1967)], and 5 - p - methoxyphenyl-2-indancarboxylic acid [M. Minnsen-Guetté, M. Dvolaitzky, and J. Jacques, Bull Soc. Chim. France, No. 5, 2111 (1968)] haxe been described in the literature as being useful anti-inflammatory agents. Also described in the literature (Nature 167, p. 273, Linnell et al.) are the compounds having the formula



in which R is H or methoxy. It is reported these compounds were synthesized from the corresponding carboxylic acids by the method of Steiger and Reichstein but no further information is available.

SUMMARY OF THE AGENTS

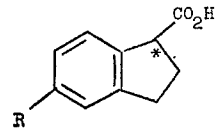
The 5-phenyl-1-indancarboxylic acids of the present invention are the compounds having the formula



or a pharmaceutically-acceptable, nontoxic salt thereof.

DISCLOSURE OF THE INVENTION

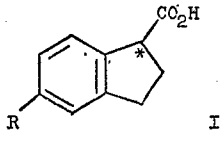
This invention relates to non-steroidal anti-inflammatory agents useful in animals, including man, which compounds are characterized by the formula



in which R is phenyl; or a nontoxic, pharmaceutically-acceptable salt thereof. The carboxyl group in the compounds of the instant invention is attached to an asymmetric carbon atom (*) such that the compounds exist in two isomeric forms; dextro- and levorotatory isomers. Both the substantially pure dextro- and levorotatory isomers of these compounds, as well as the racemic mixtures are considered to be an integral part of the invention.

It was an object of the instant invention to prepare non-steroidal anti-inflammatory agents that would be useful in the treatment of a variety of inflammatory diseases such as Rheumatoid Arthritis, Rheumatoid Spondylitis, Osteoarthritis, Gout and other similar afflictions.

These objectives have been achieved by the provision, according to the present invention, of the compound having the formula



I

in which R is phenyl; or a nontoxic pharmaceutically-acceptable salt thereof.

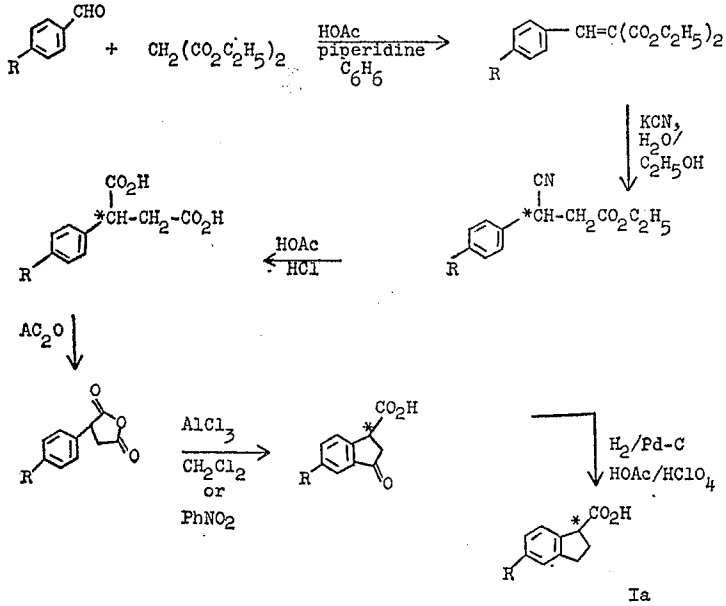
A most preferred embodiment is the levorotatory isomer having the name (—)-5-phenyl-1-indancarboxylic acid.

The pharmaceutically-acceptable, nontoxic salts are those having metallic cations such as sodium, potassium, calcium and aluminum and organic amine cations of trialkylamines, e.g. triethylamine, procaine, dibenzylamine, N-benzyl-β-phenethylamine, 1-ephenamine, N,N'-dibenzylethylenediamine, dehydroabietylamine, N,N'-bis-dehydroabietylethylenediamine, N-(lower)alkylpiperidines, e.g. N-ethylpiperidine, and other amines which have been used to form salts with medicinally active carboxylic acids.

The term "(lower)alkyl" as used herein means both straight and branched chain aliphatic hydrocarbon radicals having from 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, etc. Similarly,

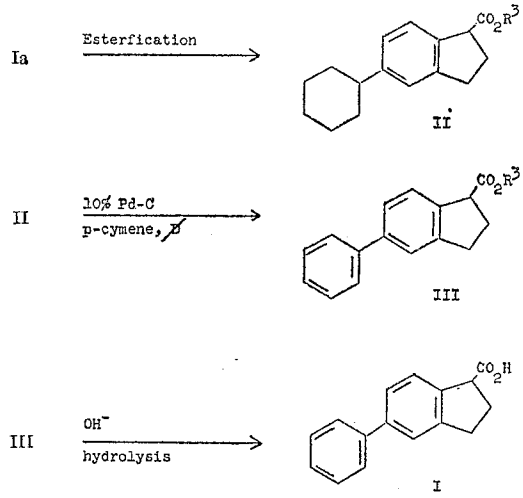
where the term "(lower)" is used as part of the description of another group, e.g. "(lower)alkoxy," it refers to the alkyl portion of such group which is therefore as described above in connection with "(lower)alkyl" and thus includes such radicals as methoxy, ethoxy, isopropoxy, etc.

The compounds of the instant invention can be prepared by the following synthesis:



wherein R is cyclohexyl.

The 5-cyclohexyl-1-indancarboxylic acid (Ia) is further treated to prepare the claimed compounds of the instant invention:



The compounds of the instant invention can be resolved into their substantially pure dextro- and levorotatory isomers by methods commonly known in the art. For illustrative purposes, the intermediate compound 5-cyclohexyl-1-indancarboxylic acid (Ia) was resolved into its respective isomers by the procedure of first treating the mixture with cinchonidine to produce the cinchonidine salt of (+)-5-cyclohexyl-1-indancarboxylic acid. The salt was recrystallized and then decomposed to the free acid to yield substantially pure (+)-5-cyclohexyl-1-indancarboxylic acid.

The levorotatory acid enriched mother liquors remaining above, after the collection of the cinchonidine salt of the dextrorotatory acid was isolated from it, were concentrated to dryness. The residue was treated with ether and hydrochloric acid. A partially resolved mixture of

the dextrorotatory and levorotatory isomers, enriched with the levorotatory acid, was obtained.

The enriched acid was dissolved in ethanol and treated with dehydroabietylamine. The dehydroabietylamine salt of (—)-5-cyclohexyl-1-indancarboxylic acid was collected and purified by crystallization. The salt was treated with hydrochloric acid and extracted with ether. The ethereal solution was concentrated to dryness and the substantially pure levorotatory isomer was crystallized from petroleum ether. Subsequent treatment of the resolved levo- or dextrorotatory 5 - cyclohexyl - 1 - indancarboxylic acid with Pd/C and p-cymene as shown above produces respectively the levo- or dextrorotatory 5-phenyl-1-indancarboxylic acid.

The racemic mixture, (±)-5-phenyl-1-indancarboxylic acid, can be resolved by treating the racemic acid with (+)-α-(1-naphthyl)ethylamine in benzene to produce the (+)-5-phenyl-1-indancarboxylic acid-(naphthyl)ethylamine salt. Acidic treatment of the salt produced the substantially pure (+)-5-phenyl-1-indancarboxylic acid (see Example 3).

The (—)isomer enriched mother liquors were treated with (—α-(1 - naphthyl)ethylamine in a similar manner as above to produce the substantially pure (—)-5-phenyl-1-indancarboxylic acid (see Example 4).

All the acidic compounds of the instant invention can be resolved into their component dextrorotatory and levorotatory isomers by a procedure similar, if not identical, to that described above. Examination of the chemical literature likewise provided many other methods for the resolution of racemic monocarboxylic acids.

Some racemic mixtures can be precipitated as eutectics instead of mixed crystals and can thus be quickly separated and in such cases can sometimes be selectively precipitated. The more common method of chemical resolutin may be used. By this method diastereoisomers are formed from the racemic mixture by reaction with an optically-active resolving agent. Thus, an optically-active base can be reacted with the carboxyl group. The difference in solubility between the diastereoisomers formed permits the selective crystallization of one form and regeneration of the optically-active acid from the salt. There is, however, a third method of resolving which shows great promise. This is one of the other forms of biochemical procedures using selective enzymatic reaction. Thus, the racemic acid can be subjected to an asymmetric oxidase or decarboxylase which will, by oxidation or decarboxylation, destroy one form, leaving the other form unchanged. Even more attractive is the use of hydrolylase on derivative of the racemic mixture to form preferential-

ly one form of the acid. Thus, esters or amides of the acids can be subjected to an esterase or amidase which will selectively saponify one enantiomorph and leave the other unchanged. Amide or salt disastereoisomers of the free acid may be formed with optically-active amines, such as quinine, brucine, cinchonidine, cinchonine, dehydroabietylamine, hydroxy-hydrindamine, methylamine, morphine, α-phenylethylamine, phenyloxynaphthylmethylamine, quinidine, 1-fenchylamine, strychnine, basic amino acids, such as lysine, arginine, amino acid esters, and the like. Similarly, ester disastereoisomers of the free acid may be formed with optically-active alcohols, such as borneol, methanol, 2-octanol and the like. Especially preferred is the use of cinchonidine to give the readily decomposable disastereoisomer salt which may then be resolved by dissolving in a solvent, such as acetone, and distilling the solvent at atmospheric pressure until crystals begin to appear and further crystallization produced by allowing the mixture to cool to room temperature, thereby separating the two enantiomorphs. The acid may be recovered from the salt by extracting the salt between an organic solvent, such as petroleum ether and dilute hydrochloric acid or some other organic solvent-aqueous system. Workup of the remaining mother liquors and subsequent purification will usually provide the other isomer.

It is noted, however, the racemic compounds of the present invention are themselves potent anti-inflammatory agents.

The compounds of this invention have a high degree of anti-inflammatory activity. They are useful in treating arthritis, rheumatism and other inflammatory diseases in mammals.

Anti-inflammatory tests of the compounds of the present invention were carried out on rats using the carrageenin-induced foot edema test of Charles A. Winter et al., "Carrageenin-Induced Edema in Hind Paw of the Rat as an Assay for Anti-Inflammatory Drugs," Proceedings of the Society for Experimental Biology and Medicine, 111, 544 (1962). The compound under investigation was given orally to the rat, and one hour later carrageenin was injected subcutaneously into one paw. Three hours later the degree of edema was measured volumetrically by fluid displacement, and compared to that of the control paw to give a result presented in terms of percentage inhibition of edema. Any result of more than 30% inhibition was greater than three times the standard deviation of the result in control animals, and thus clearly indicated anti-inflammatory activity.

In the rat paw edema test described above, the compounds of the instant invention exhibit anti-inflammatory activity deemed useful in the treatment of inflammatory diseases in mammals, including man. The compounds of the invention are generally useful in the dosage range of about 0.1 mg./kg. to about 40 mg./kg. three to four times a day.

They can be administered orally or parenterally, but preferably orally. More specifically, the compounds of the instant invention are preferentially administered in dosages in the range of about 0.2 mg./kg. to about 30 mg./kg. three to four times a day.

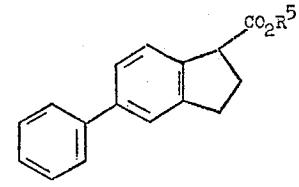
The dosage will vary with the particular compound of the invention. For example the racemic mixture (±)-5-phenyl-1-indancarboxylic acid, produced inhibition of edema at a minimum effective dose (MED) of 4.5 mg./kg. (MED is defined as the dose which produced 30% inhibition of edema).

The (−)-5-phenyl-1-indancarboxylic acid produced inhibition of edema with a MED of 3.5 mg./kg. On the other hand, (+)-5-phenyl-1-indancarboxylic acid was essentially ineffective with a MED above 32 mg./kg. The unresolved racemic mixture is active and is useful as an anti-inflammatory agent.

The oral dosage in humans of the compounds of the present invention is in the range of about 0.2 mg./kg. to about 25 mg./kg. administered three or four times a day. The preferred human dosage is in the range of 0.2 mg./kg. to about 10 mg./kg. three to four times a day.

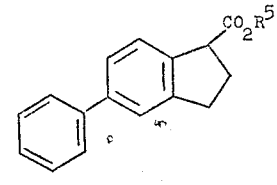
The carboxylic acids I of the present invention also show activity in mice, rats and dogs when administered in the form of their (lower)alkyl esters or tertiary-amino (lower)alkyl esters. These compounds are also considered an integral part of the present invention.

Therefore, a preferred embodiment of the present invention are the compounds having the formula



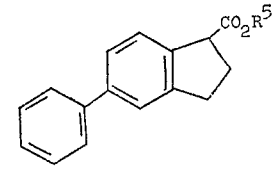
in which R^5 is (lower)alkyl or a (lower)alkyl possessing a t-amine function; or a pharmaceutically acceptable salt thereof.

Another preferred embodiment are the compounds having the formula



in which R^5 is (lower)alkyl.

A more preferred embodiment are the compounds having the formula



in which R^5 is methyl, ethyl or propyl.

For the purpose of this disclosure, the term "(lower) alkyl possessing a t-amine function" shall mean a group consisting of up to 8 carbon atoms, which group contains a t-amine function, i.e. N,N-dimethylaminoethyl-, N,N-diethylaminoethyl-, N-methyl-4-piperidyl-, N-ethyl-4-pyrrolidyl-, N-methyl-3-pyrrolidyl-, N,N-dimethylaminopropyl-, or the like.

When the compounds of the present invention contain an ester function possessing a tertiary amine function, the compounds are capable of forming acid addition salts such as the hydrochloride, hydrobromide, hydroiodide, sulfate, sulfamate, and phosphate, and the organic acid addition salts such as the maleate, acetate, citrate, succinate, benzoate, tartrate, malate, mandelate, ascorbate and the like. All of these salts and their equivalents are a part of the invention.

The ester, (±)-methyl 5-phenyl-1-indanecarboxylate, had an MED of 4 mg./kg. in rats.

PREPARATION OF STARTING MATERIALS

(A)

(1) p-Cyclohexylbenzaldehyde: [D. Bodroux and R. Thomassin, Compt. Rend., 205, 991 (1937)]

Titanium tetrachloride [A. Rieche, H. Gross, and E. Höft, Organic Syntheses, 47, 1 (1967)] (183 ml., 316 grams, 1.67 moles) was added slowly over a period of ten minutes and with constant stirring to a cooled (ice-water) solution of cyclohexylbenzene (160 grams, 1.0 mole) in methylene chloride (650 ml.). With continued stirring and cooling, dichloromethyl methyl ether (96 grams, 0.833 mole) was added dropwise over a period of 45 minutes. After the addition was complete, the mixture was stirred for thirty minutes with cooling, followed by 130 minutes

at room temperature. The reaction mixture was poured onto ice. The organic layer was separated and the aqueous layer extracted with methylene chloride (3× 250 ml.). The combined methylene chloride solution was washed with water (2× 400 ml.) and dried (sodium sulfate). The dried solution was reduced to dryness in a rotary evaporator to leave a brown oil (209 grams). The oil was distilled under reduced pressure. p-Cyclohexylbenzaldehyde (81.3 grams, 52%) was collected as the fraction with B.P. 98–100°/0.2 mm. [lit. D. Bodroux and R. Thomassin, Compt. Rend., 205, 991 (1937)—M.P. 159°/10 mm.].

(2) Diethyl p-cyclohexylbenzylidenemalonate

A solution of p-cyclohexylbenzaldehyde (9.4 grams, 0.05 mole), diethyl malonate (8.01 grams, 0.05 mole), piperidine (0.5 grams), and glacial acetic acid (0.33 gram) in benzene (25 ml.) was heated under reflux for 18 hours [C. F. H. Allen and F. W. Spangler, "Organic Syntheses," Coll. vol. III, John Wiley and Sons Inc., New York, N.Y., 1963, p. 377]. The liberated water was removed from the reaction mixture as it was formed The cooled reaction mixture wis diluted with benzene (25 ml.), washed with water (2× 25 ml.) followed by 1 N hydrochloric acid (25 ml.), water (25 ml.), saturated sodium bicarbonate solution (25 ml.), and water (25 ml.). The solution was dried (sodium sulfate) and concentrated in a rotary evaporator to leave a yellow oil (17.7 g.). The product was distilled under vacuum. Diethyl p-cyclohexylbenzylidenemalonate (11.7 grams, 71%) was collected as the fraction with B.P. 172–174°/0.01 mm.

Analysis.—Calc'd for $C_{20}H_{26}O_4$ (percent): C, 72.70; H, 7.93. Found (percent): C, 72.62; H, 7.94.

(3) Ethyl 3-cyano-3-(p-cyclohexylphenyl)propionate

A solution of potassium cyanide (1.8 grams, 0.0277 mole) in water (4.5 ml.) was added quickly to a solution of diethyl p-cyclohexylbenzylidenemalonate (9.0 grams, 0.0272 mole) in 100% ethanol (90 ml.). The stirred mixture was heated by means of an oil bath maintained at about 70° for twenty hours [C. F. H. Allen and H. B. Johnson, "Organic Syntheses," Coll. vol. IV, John Wiley and Sons, Inc., New York, N.Y., 1963, p. 804]. The reaction mixture was allowed to cool to room temperature. The precipitated solid was removed by filtration. The filtrate was acidified with 10% hydrochloric acid (1.5 ml.) and then concentrated in a rotary evaporator. The residue was partitioned between chloroform (150 ml.) and water (50 ml.). The chloroform layer was separated, dried (sodium sulfate) and concentrated to leave a pale yellow oil (8.1 grams) which was distilled under reduced pressure. Ethyl 3-cyano-3-(p-cyclohexylphenyl)propionate (4.2 grams, 54%) was collected as the fraction with B.P. 160–161°/0.15 mm.

Analysis.—Calc'd for $C_{18}H_{23}NO_2$ (percent): C, 75.75; H, 8.12. Found (percent): C, 75.77; H, 8.28.

(4) p-Cyclohexylphenylsuccinic acid

A mixture of ethyl 3-cyano-3-(p-cyclohexylphenyl)-propionate (3.5 grams), glacial acetic acid (10 ml.) and concentrated hydrochloric acid (10 ml.) was heated under reflux for three hours. A crystalline solid separated from the reaction mixture which was allowed to cool slowly. The solid (1.95 grams, 67%), with M.P. 178–182°, was recrystallized from aqueous ethanol followed by ethyl acetate to give the p-cyclohexylphenylsuccinic acid as colorless crystals, M.P. 188–189° C.

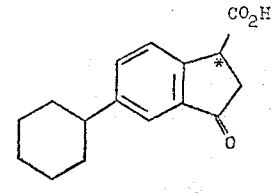
Analysis.—Calc'd for $C_{16}H_{20}O_4$ (percent): C, 69.54; H, 7.30. Found (percent): C, 69.54; H, 7.36.

(5) p-Cyclohexylphenylsuccinic anhydride

A mixture of p-cyclohexylphenylsuccinic acid (10.0 grams) and acetic anhydride (50 ml.) was heated under reflux for 1.25 hours. The cooled solution was reduced to dryness in a rotary evaporator and the solid residue recrystallized from cyclohexane to give p-cyclohexylphenylsuccinic anhydride (8.8 grams, 94%) as colorless crystals, M.P. 116.5–118° C. The product was recrystallized from cyclohexane to give colorless crystals, M.P. 117–118.5° C.

Analysis.—Calc'd for $C_{16}H_{18}O_3$ (percent): C, 74.39, H, 7.02. Found (percent): C, 74.58; H, 7.24.

(6) (±)-5-cyclohexyl-3-oxo-1-indancarboxylic acid

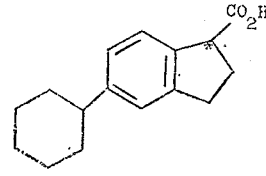


A solution of p-cyclphexylohenylsuccinic anhydride (33.0 grams, 0.128 mole) in dry methylene chloride (400 ml.) was added dropwise to a stirred, cooled (ice-water) suspension of aluminum chloride (37.4 grams, 0.281 mole) in methylene chloride (400 ml.) [H. O. House, F. J. Sauter, W. G. Kenyon, and J. J. Riehl, J. Org. Chem., 33, 957 (1968)].

The mixture was stirred with cooling for one hour, and was then stirred at room temperature for twenty-four hours. The reaction mixture was reduced to dryness and the residue triturated with ice-water (500 ml.) and concentrated hydrochloric acid (30 ml.). The resulting gummy suspension was stirred for thirty-six hours at room temperature. The mixture was filtered and the collected off-white solid dried under vacuum. The solid was recrystallized from cyclohexane to give (±)-5-cyclohexyl-3-oxo-1-indancarboxylic acid (30.4 grams, 92%) as off-white crystals, M.P. 117–118° C. A portion of the product was recrystallized (with charcoal treatment) from cyclohexane to give colorless crystals, M.P. 117–118° C.

Analysis.—Calc'd for $C_{16}H_{18}O_3$ (percent): C, 74.39; H, 7.02. Found (percent): C, 74.29; H, 7.23.

(7) (±)-5-cyclohexyl-1-indancarboxylic acid



A solution of (±)-5-cyclohexyl-3-oxo-1-indancarboxylic acid (9.0 grams) in glacial acetic acid (150 ml.) containing 60% perchloric acid (2 ml.) and 10% palladium on carbon (2.0 grams) was shaken with hydrogen (Parr hydrogenator, 3 atoms) until no further hydrogen was absorbed. The mixture was filtered and anhydrous sodium acetate (2.5 grams) was added to the filtrate. The resulting solution was reduced to dryness. Several portions of toluene were added to the residue and after each addition the mixture was evaporated. The residue was partitioned between diethyl ether (200 ml.) and water (40 ml.). The ether layer was washed with water (40 ml.) followed by saturated aqueous sodium chloride (40 ml.), and dried (sodium sulfate). The solution was reduced to dryness to yield a buff solid which was recrystallized from Skellysolve B to give (±)-5-cyclohexyl-1-indancarboxylic acid (8.4 grams, 98.5%) as buff crystals. M.P. 145–147° C. A portion of the product was recrystallized from Skellysolve B (essentialy n-hexane, B.P. *0–68° C.), with charcoal treatment, to give colorless crystals, M.P. 147–148° C.

Analysis.—Calc'd. for $C_{16}H_{20}O_2$ (percent): C, 78.65; H, 8.25. Found (percent): C, 78.58; H, 8.34.

(8) Sodium 5-cyclohexyl-1-indancarboxylate (±) racemic mixture

A solution of sodium 2-ethylhexanoate (6.15 grams, 0.37 mole) in acetone (30 ml.) was added to a solution of (±)-5-cyclohexyl-1-indancarboxylic acid (9.0 grams, 0.0368 mole) in warm acetone (70 ml.). The mixture was allowed to stand and cool to room temperature. The crystalline solid (7.25 grams, 74%) that formed was collected, washed with acetone and recrystallized from methanol-acetone to give sodium 5-cyclohexyl-1-indancarboxylate as colorless crystals.

Analysis.—Calc'd for $C_{16}H_{19}NaO_2$ (percent): C, 72.16; H, 7.19. Found (percent): C, 72.11; H, 7.40.

(9) (±)-Methyl-5-cyclohexyl-1-indancarboxylic

Excess diazomethane in diethyl ether was added to a suspension of (±)-5-cyclohexyl-1-indancarboxylic acid (18.0 g.) in diethyl ether (100 ml.). The resulting solution was concentrated to an oil which slowly crystallized on standing to give a buff solid (19.5 g.), M. P. 44.5–46.5° C. The product was recrystallized from methanol after treatment with activated charcoal to give colorless crystals (18.2 g.) M.P. 46.5–48° C.

Analysis.—Calc'd for $C_{17}H_{22}O_2$ (percent): C, 79.03; H, 8.58. Found (percent): C, 78.88; H, 8.74.

(10) Resolution of (±)-5-cyclohexyl-1-indancarboxylic acid

(A) (+)-5-cyclohexyl-1-indancarboxylic acid.—A solution of (±)-5-cyclohexyl-1-indancarboxylic acid (15.0 grams, 0.0614 mole) and cinchonidine (9.05 grams, 0.0307 mole) in absolute ethanol (700 ml.) was boiled down to a volume of about 300 ml. The mixture was allowed to cool slowly and was left for twenty hours at 25° C. The colorless crystals were collected and washed with cold ethanol to give the cinchonidine salt of (+)-5-cyclohexyl-1-indancarboxylic acid (13.0 grams), M.P. 212–212.5° C. Additional cinchonidine (1.0 gram, 0.0034 mole) was added to the mother liquors and their volume reduced to about 165 ml. by boiling. The hot solution was seeded with the salt of the (+) acid and stored at 5° C. for sixty-five hours, when an additional crop (2.4 grams) of the cinchonidine salt of the (+) acid, M.P. 211–215° C. was obtained. The mother liquors were retained for isolation of the (—) isomer.

The salt with M.P. 212–212.5° C. was recrystallized from ethanol to give colorless crystals (11.8 grams), M.P. 217.5–219° C. The product was partitioned between ether (500 ml.) and 10% aqueous hydrochloric acid (250 ml.). The ethereal layer was washed successively with 10% aqueous hydrochloric acid (250 ml.), water (2× 250 ml.) and water saturated with sodium chloride (250 ml.). The ethereal solution was dried (Na_2SO_4), filtered, and the filtrate reduced to dryness to give (+)-5-cyclohexyl-1-indancarboxylic acid (5.5 grams), M.P. 108–110° C. Two recrystallizations from petroleum ether (B.P. 39–50° C.), gave colorless needles, M.P. 108–109.5° C., $[\alpha]_D^{25}$ +9.60° (ethanol), and

$[\alpha]_{365}^{25}$

+44.8° (ethanol).

Analysis.—Calc'd for $C_{16}H_{20}O_2$ (percent): C, 78.65; H, 8.25. Found (percent): C, 78.40; H, 8.27.

(B) (—) - 5 - cyclohexyl-1-indancarboxylic acid.—The mother liquors from the salt formation in part A, were reduced to dryness and the residue treated with ether and 10% aqueous hydrochloric acid as previously described for the salt of the (+) isomer and from the ethereal layer was obtained a partially resolved mixture of acids (7.6 grams), enriched in the (—) isomer, $[\alpha]_D^{25}$ —7.69° (ethanol) and

$[\alpha]_{365}^{25}$

—35.4° C. (ethanol). This mixture was extracted with boiling petroleum ether (B.P. 39–50° C., 3× 35 ml.) and the combined extracts were reduced in volume (50 ml.) and cooled in an ice bath. The crystalline solid (5.1 grams), M.P. 105–108° C., $[\alpha]_D^{25}$ —8.91° (ethanol) and

$[\alpha]_{365}^{25}$

—41.5° (ethanol), was collected.

The solution of this acid (5.02 grams, 0.0205 mole) and dehydroabietylamine (5.85 grams, 0.0205 mole) in ethanol (500 ml.) was boiled down to a volume of about 175 ml. and cooled to 25° C. during two hours. The dehydroabietylamine salt of (—)-5-cyclohexyl-1-indancarboxylic acid (8.7 grams), M.P. 179–181° C., was collected and recrystallized from ethanol to give colorless crystals (8.0 grams), M.P. 184–185° C. The mother liquors from the product with M.P. 179–181° C., were reduced in volume and an additional crop of salt (0.95 grams), M.P. 178.5–180.5° C., was isolated. This latter material was recrystallized from ethanol and the product (0.78 gram), M.P. 182–183° C., was combined with the main crop. The dehydroabietylamine salt (8.78 grams) was partitioned between ether (400 ml.) and 10% aqueous hydrochloric acid. The ethereal solution was washed with water (3× 150 ml.) followed by water saturated with sodium chloride (2× 100 ml.), dried ($NaSO_4$), and reduced to dryness to leave the (—) isomer (4.0 grams). Recrystallization from petroleum ether (B.P. 39–50° C.) gave colorless needles (3.41 grams) of (—)-5-cyclohexyl-1-indancarboxylic acid: M.P. 108–109.5° C., $[\alpha]_D^{25}$ —9.66° (ethanol) and

$[\alpha]_{365}^{25}$

—44.7° (ethanol).

Analysis.—Calc'd for $C_{16}H_{20}O_2$ (percent): C, 78.65; H, 8.25. Found (percent): C, 78.85; H, 8.31.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

EXAMPLE 1

(±)-Methyl 5-phenyl-1-indancarboxylate.—A mixture of (±)-methyl 5-cyclohexyl-1-indancarboxylate (14.5 g.) and 10% palladium on carbon (7.0 g.) in p-cymene (230 ml.) was heated under reflux for 42 hours. The reaction mixture was cooled and filtered to remove the catalyst. The filtrate was concentrated in a rotary evaporator to leave an orange oil which was crystallized from petroleum ether (B.P 30–60°) to give (±)-methyl 5-phenyl-1-indancarboxylate (11.1 g., 78%) as off-white crystalls, M.P. 44–47°. A portion of the product was recrystallized twice from petroleum ether to give off-white crystals, M.P. 48.5–50°.

Analysis.—Calc'd for $C_{17}H_{16}O_2$ (percent): C, 80.92; H, 6.39. Found (percent): C, 81.04; H, 6.61.

EXAMPLE 2

(±)-5-phenyl-1-indancarboxylic acid.—A solution of 10% aqueous sodium hydroxide (30 ml.) was added to a solution of (±)-methyl 5-phenyl-1-indancarboxylate (8.0 g.) in ethanol (32 ml.), and the mixture was heated under reflux for 5 minutes. The mixture was cooled and then poured into cold water (250 ml.). The resulting solution was acidified with ice-cooling to pH 2 with 10% hydrochloric acid. The precipitated solid was washed with cold water, dried, and recrystallized from methanol with charcoal treatment to give (±)-5-phenyl-1-indancarboxylic

acid (6.2 g., 82%) as off-white crystals, M.P. 148–151°. The product was recrystallized from methanol followed by cyclohexane to give off-white crystals, M.P. 134–136°, resolidifying and remelting at 150.5–152°.

Analysis.—Calc'd for $C_{16}H_{14}O_2$ (percent): C, 80.64; H, 5.92. Found (percent): C, 80.35; H, 5.99.

EXAMPLE 3

(+)-5-phenyl-1-indancarboxylic acid.—A mixture of (±)-5-phenyl-1-indancarboxylic acid (5.0 g., 0.021 mole) and (+)-α-(1-naphthyl)ethylamine (3.59 g., 0.021 mole) in benzene (100 ml.) was boiled for about 5 minutes. The hot solution was filtered to remove a small amount of insoluble material, and the filtrate boiled down to a volume of about 35 ml. when boiling Skellysolve B (70 ml.) was added. The mixture was allowed to stand at 25° C. for three hours. The solid material was collected, washed well with cold benzene:Skellysolve B (1:2), and dried to give a salt (7.5 g.), M.P. 162–168° with prior softening. The mother liquors (A) were retained. The salt was recrystallized twice from benzene:Skellysolve B to give colorless crystals (3.3 g.), M.P. 178–179°. The mother liquors (B) from the first recrystallization were retained. The salt was partitioned between diethyl ether (70 ml.) and 0.5 N hydrochloric acid (40 ml.). The ether solution was washed with water followed by saturated aqueous sodium chloride, dried (Na_2SO_4), and reduced to dryness. The residue (2.0 g.), M.P. 136–138.5°, was recrystallized twice from cyclohexane to give (+)-5-phenyl-1-indancarboxylic acid (1.55 g.) as colorless crystals: M.P. 139–140°; $[\alpha]_D^{25}$ +13.56° (ethanol), and

$$[\alpha]_{365}^{25}$$

+85.7° (ethanol).

Analysis.—Calc'd for $C_{16}H_{14}O_2$ (percent): C, 80.64; H, 5.92. Found (percent): C, 80.43; H, 6.01.

EXAMPLE 4

(—)-5-phenyl-1-indancarboxylic acid. — The mother liquodrs A and B from Example 3 were combined and flashed to dryness. The salts were treated with dilute hydrochloric acid, as described in Example 3, to liberate acids (2.8 g.) enriched in the (—) isomer. A solution of (—)-α-(1-naphthyl)ethylamine (2.015 g., 0.01175 mole) in benzene (50 ml.) was added to a boiling solution of the acids (2.8 g., 0.01175 mole) in benzene (100 ml.). Skellysolve B (125 ml.) was added to the boiling solution, and the mixture allowed to stand at room temperature for 2 hours. The salt (3.8 g., M.P. 178–179°) which crystallized was treated with dilute hydrochloric acid, as described in Example 3, to liberate the free acid. The product was recrystallized from cyclohexane to give (—)-5-phenyl-1-indancarboxylic acid (1.8 g.) as colorless crystals, M.P. 139–140.5°. Recrystallization from cyclohexane gave colorless crystals, M.P. 139–140.5°; $[\alpha]_D^{25}$ —13.53° (ethanol), and

$$[\alpha]_{365}^{25}$$

—85.0° (ethanol).

Analysis.—Calc'd for $C_{16}H_{14}O_2$ (percent): C, 80.64; H, 5.92. Found (percent): C, 80.86; H, 5.91.

EXAMPLE 5

(±)-Ethyl 5-phenyl-1-indancarboxylate.—A solution of (±)-5-phenyl-1-indancarboxylic acid (6.0 g.) in ethanol (30 ml.) containing hydrogen chloride (9.0 g.) is heated under reflux for 4.5 hours. The cooled solution is diluted with water, and the ethanol removed in a rotary evaporator. The residual aqueous mixture is extracted with diethyl ether. The ether extract is washed with aqueous sodium bicarbonate followed by water and saturated aqueous sodium chloride, dried (Na_2SO_4), and concentrated. The residual oil is distilled to give (±)-ethyl 5-phenyl-1-indancarboxylate.

EXAMPLE 6

(±)-N-methyl - 4 - piperidyl - 5 - phenyl-1-indancarboxylate hydrochloride.—A solution of (±)-5-phenyl-1-indancarboxylic acid (0.0284 mole), thionyl chloride (0.0294 mole), and dimethylformamide (3 drops) in methylene chloride (75 ml.) is heated under reflux for one hour. The solution is concentrated in a rotary evaporator. A solution of the residual oil in benzene (20 ml.) is added dropwise, with cooling, to a solution of 4-hydroxy-N-methylpiperidine (0.0573 mole) in benzene (30 ml.) over a period of ten minutes. The mixture is stirred at room temperature for an additional 15 minutes. Water (25 ml.) followed by saturated aqueous sodium bicarbonate (50 ml.) is added to the mixture, which is stirred for 15 minutes. The benzene layer is separated, washed twice with water, dried (Na_2SO_4), and concentrated to an orange oil. Hydrogen chloride gas is passed into a solution of the oil in diethyl ether (100 ml.) until no further material precipitated from solution. The supernatant ether is decanted, and the residual gum washed with fresh ether and then triturated with ethyl acetate to give a crystalline solid. The product is recrystallized to give (±)-N-methyl-4-piperidyl-5-phenyl-1-indancarboxylate hydrochloride.

EXAMPLE 7

(±)-β-dimethylaminoethyl 5 - phenyl - 1 - indancarboxylate hydrochloride.—In a manner similar to that described in Example 6, (±) - β - dimethylaminoethyl 5-phenyl-1-indancarboxylate hydrochloride is prepared from (±)-5-phenyl-1-indancarboxylic acid (0.0284 mole), thionyl chloride (0.0294 mole), β-dimethylaminoethanol (0.0573 mole) and hydrogen chloride. The crude hydrochloride is recrystallized to produce the pure product.

EXAMPLE 8

(—)-Methyl 5-phenyl-1-indancarboxylate.—Excess diazomethane in diethyl ether is added to an ice-cold solution of (—)-5-phenyl-1-indancarboxylic acid (6.0 g.) in diethyl ether (50 ml.). The solution is filtered and concentrated to 75 ml. The solution is washed with saturated aqueous sodium bicarbonate followed by water and saturated aqueous sodium chloride, dried (Na_2SO_4), and concentrated in a rotary evaporator. The residual oil is distilled to give (—)-methyl 5-phenyl-1-indancarboxylate.

EXAMPLE 9

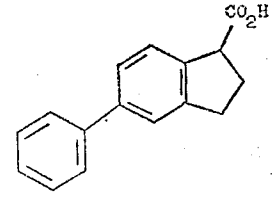
(—)-Methyl 5-cyclohexyl-1-indancarboxylate.—Substitution into the procedures of Example 8 for the (—)-5-phenyl-1-indancarboxylic acid used therein of (—)-5-cyclohexyl-1-indancarboxylic acid produces (—)-methyl 5-cyclohexyl-1-indancarboxylate.

EXAMPLE 10

(—)-5-Phenyl-1-indancarboxylic acid. — Substitution into the procedure of Example 1 for the (±)-methyl 5-cyclohexyl-1-indancarboxylic acid used therein of (—)-methyl 5-cyclohexyl - 1 - indancarboxylic acid produces (—)-methyl 5-phenyl-1-indancarboxylate. Hydrolysis of this ester with sodium hydroxide as in Example 2 produces (—)-5-phenyl-1-indancarboxylic acid.

We claim:

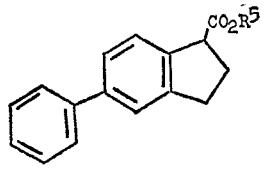
1. A compound having the formula



or a nontoxic, pharmaceutically-acceptable salt thereof.

2. The levorotatory isomer of the compound of claim 1.

3. A compound having the formula



in which R^5 is a radical selected from the group comprising (lower)alkyl, N,N-di(lower)alkylamino(lower) alkyl-, N-(lower)alkyl-4-piperidyl-, N - (lower)alkyl-4-pyrrolidyl- or N-(lower)alkyl-3-pyrrolidyl; or a pharmaceutically acceptable salt thereof.

4. The compounds of claim 3 wherein R^5 is (lower) alkyl.

5. The compounds of claim 3 wherein R^5 is methyl, ethyl or propyl.

References Cited

UNITED STATES PATENTS

3,565,943 2/1971 Juby et al. ..... 260—469 X

OTHER REFERENCES

Bulletin de La Société Chemique de France 1968, No. 5, Dvolaitzky et al., pp. 2111–2117.

LORRAINE A. WEINBERGER, Primary Examiner

J. L. DAVISON, Assistant Examiner

U.S. Cl. X.R.

260—283 R, 284, 285, 294.3 A, 326.3, 343.7, 346.8, 448 R, 465 D, 475 SC, 501.1, 501.11, 515 R, 558 R; 424—316, 317