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TRIFLUOROMETHYLPYRAZOLOINDENONE DERIVATIVES

Bernard Loev, Broomall, Pa., and William A. Mosher, Newark, Del., assignors to Smith Kline & French Laboratories, Philadelphia, Pa., a corporation of Pennsylvania

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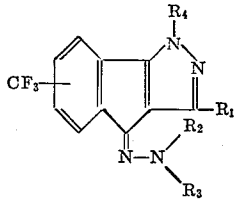
11 Claims. (Cl. 260—310)

This invention relates to new trifluoromethylpyrazoloindenone, hydrazone derivatives which have useful pharmacodynamic activity and also to the trifluoromethylpyrazoloindenone intermediates.

More specifically, this invention relates to trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazones having utility in the animal organism particularly as tranquilizers and ataractics. In addition these compounds are useful as anti-Parkinson agents, hypotensive agents and general central nervous system depressants. The trifluoromethylpyrazolo[3,4-a]inden-4(1H)-ones of particular utility as intermediates in the preparation of the corresponding hydrazones of this invention, also are useful as mild sedatives and tranquilizers and as antibacterial agents against gram-positive organisms.

The new trifluoromethylpyrazoloindenone, hydrazones of this invention are represented by the following fundamental structural formula:

FORMULA I



when:

R_1 represents alkyl having 1 to 8 carbon atoms inclusive, alkenyl having 2 to 8 carbon atoms inclusive, benzyl, phenethyl, phenyl, substituted phenyl such as aminophenyl, halophenyl, lower alkyl phenyl or lower alkoxy phenyl, cycloalkyl, and cycloalkenyl, said cycloalkyl moiety having 3 to 6 carbon atoms, inclusive, and said cycloalkenyl moiety having 4 to 6 carbon atoms, inclusive;

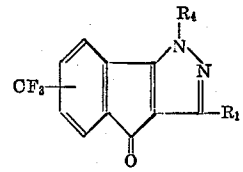
R_2 and R_3 represent hydrogen, lower alkyl or when taken together with the nitrogen atom to which they are attached, monophenylamino; and

R_4 represents hydrogen, lower alkyl, aralkvl having 7 to 8 carbon atoms such as benzyl or phenethvl, acyl of less than 9 carbon atoms such as benzenesulfonyl or benzoyl, lower alkanoyl such as acetyl or propionyl, or alkyloxycarbonyl such as carbethoxy or carbomethoxy.

Preferred compounds of this invention are those of Formula I in which R_2, R_3 and R_4 are hydrogen, R_1 is alkyl having 1 to 5 carbon atoms inclusive, alkenyl having 2 to 5 carbon atoms inclusive or cycloalkyl having 3 to 6 carbon atoms, inclusive.

The novel trifluoromethylpyrazoloindenone intermediates, also objects of this invention, are represented by the following structural formula:

FORMULA II



in which R_1 and R_4 are as defined for Formula I. These compounds are particularly useful when R_4 is hydrogen and R_1 is alkyl having 1 to 5 carbon atoms inclusive, alkenyl having 2 to 5 carbon atoms inclusive, or cycloalkyl having 3 to 6 carbon atoms, inclusive.

The terms "lower alkyl," "lower alkoxy" or "lower alkanoyl" are used herein to indicate moieties with not more than 4 carbon atoms, preferably 1 or 2 carbon atoms.

Whenever basic or acidic producing moieties are present in the compounds of this invention the corresponding nontoxic, chemically stable and pharmaceutically acceptable salts are included in this invention such as the acid addition salts of an amino substituent.

The trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one derivatives of this invention are advantageously prepared from trifluoromethyl-2-acyl-1,3-indandiones by reaction with various molar equivalents of hydrazine. For instance, reaction of the substituted indandione with about one molar equivalent of hydrazine yields the trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one intermediates of Formula II. This reaction is preferably carried out at elevated temperatures, such as from about 40° C. to 130° C., for a reaction period of from about 30 minutes to 24 hours in a suitable solvent in which the reactants are substantially soluble and with which no chemical reaction occurs. Usually a polar organic solvent is used such as the preferred lower alcohols especially methanol and ethanol or mixtures thereof. Alternatively, however, benzene, tetrahydrofuran, toluene, xylene or other such solvents can be used. The hydrazine reactant may be either pure hydrazine or the hydrate.

Small amounts of hydrazone impurities are formed as byproducts in some cases. The reaction mixture is conveniently worked up by diluting the mixture with water, separating the resulting solid and fractionally crystallizing the trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one intermediate of Formula II.

The compounds in which R_4 is alkyl, aralkyl or acyl are preferably prepared by reacting the trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one intermediate with a basic reagent, preferably an alkali metal or its hydroxide, amide, carbonate or, advantageously, hydride, to form the N-metal salt, for instance the preferred sodium, potassium or lithium derivative at the 1-position. This N-metal derivative is then reacted with a reactive alkyl, aralkyl or acyl halide to give the 1-substituted-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one compounds.

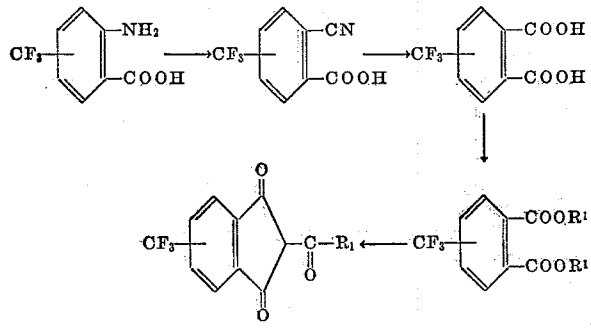
The novel hydrazones of this invention represented by Formula I are prepared by reacting the intermediate ketones of Formula II with hydrazine, either about one molar equivalent or an excess, at from about 25° C. to 140° C. for from 30 minutes to 72 hours under reaction conditions much like those described hereabove for the formation of the ketone intermediates. Methanol and ethanol are especially preferred solvents for this reaction.

This two-step reaction is necessary for compounds in which R_2, R_3 or R_4 are substituents other than hydrogen. Other compounds are preferably prepared by reacting the trifluoromethyl-2-acyl-1,3-indandione with either about 2

moles or an excess of hydrazine to form the desired 4-hydrazone end products directly. This method is preferred. The reaction conditions employed are similar to those described above for the preparation of the trifluoromethylpyrazolo[3,4-a]inden-4-one intermediates.

In these reactions an excess of hydrazine can be used and the reaction time can be extended considerably but these variations have little advantage.

The trifluoromethyl-2-acyl-1,3-indandione starting materials are conveniently prepared according to the following synthetic procedure:



R^1 is methyl or ethyl and R_1 is as previously defined in Formula I.

The trifluoromethyl-2-aminobenzoic acid is diazotized by treatment in mineral acid solution, such as sulfuric or hydrochloric acid, with sodium nitrite. The diazonium salt solution is treated with aqueous cuprous cyanide. The reaction is carried out at elevated temperatures, such as at about 50° to 60° C. for a period of about 10 to 30 minutes to give, upon cooling and filtering, trifluoromethyl-2-cyanobenzoic acid. Hydrolysis of the cyano group by treatment with 55% sulfuric acid at elevated temperatures and esterification of the resulting trifluoromethylphthalic acid by treatment with a lower alcohol, such as methanol or ethanol, and sulfuric acid gives the substituted phthalate. A methyl ketone is condensed with the above prepared trifluoromethylphthalate in an aromatic solvent such as benzene or toluene with an alkaline condensing agent such as sodium methoxide, sodium ethoxide, sodium hydride or sodium hydroxide to give the trifluoromethyl-2-acyl-1,3-indandione starting material.

Although the course of the cyclization reaction with these compounds is unknown, varying amounts of the two possible isomers differing in the position of the trifluoromethyl moiety on the benzene ring of the pyrazolo-[3,4-a]inden-4(1H)-one are formed. These isomers are separated by fractional crystallization using a suitable solvent, such as a lower alcohol, advantageously aqueous ethanol.

It will be apparent to one skilled in the art that many variations of this invention can be practiced. The following examples are designed to teach fully the preparation of the compounds of this invention and are not meant to limit the scope of this invention.

Example 1

To a mixture of 100 ml. of concentrated sulfuric acid and 600 ml. of water is added 61.5 g. of 2-amino-4-trifluoromethylbenzoic acid. The mixture is cooled to 0° C. and treated with 21.0 g. of sodium nitrite in 50 ml. of water. After standing at 5–10° C. for one hour and filtering, the diazonium solution is added slowly with stirring to a solution of cuprous cyanide, prepared by mixing a warm solution of 160 g. of copper sulfate in 400 ml. of water with 85 g. of potassium cyanide in 100 ml. of water. Sodium carbonate is also added portionwise to keep the solution from becoming acidic. The resulting mixture is heated to 50–60° C. for one hour. Cooling, filtering the precipitate and recrystallizing from aqueous ethanol gives 2-cyano-4-trifluoromethylbenzoic acid.

A mixture of 45 g. of the above prepared cyano compound and 100 ml. of 55% sulfuric acid is heated at 165° C. for 30 minutes. Cooling, pouring into ice and extracting with ether gives 4-trifluoromethylphthalic acid. This acid is refluxed with 500 ml. of methanol and ½ part of concentrated sulfuric acid for two hours. The mixture is concentrated and extracted with ether. The ether extracts are washed with sodium carbonate solution and with water, dried, concentrated and distilled to give dimethyl 4-trifluoromethylphthalate.

A mixture of 26.2 g. of dimethyl 4-trifluoromethylphthalate and 7.2 g. of methyl ethyl ketone is treated with 5.7 g. of sodium methoxide and heated on a steam bath with stirring. Toluene (100 ml.) is added. After heating ten hours, the solvent and unreacted ketone is removed in vacuo. Dissolving the residue in water, acidifying with hydrochloric acid, and extracting with ether gives 2-propionyl-5-trifluoromethyl-1,3-indandione as a viscous oil.

A mixture of 27.0 g. of the above prepared indandione, 5.0 g. of hydrazine hydrate and 250 ml. of ethanol is heated at reflux for two hours. The solution is cooled and diluted with 1 l. of cold water. The resulting solid is separated to give a mixture of 3-ethyl-6 and 7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one.

These ketones (2.6 g.) are refluxed with 1.0 g. of hydrazine in 75 ml. of ethanol for 24 hours. Cooling and fractional crystallization from aqueous ethanol separates 3-ethyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone and 3-ethyl-6-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone.

Example 2

Two grams of a mixture of 3-ethyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one and the corresponding 6-trifluoromethyl isomer, prepared as in Example 1, were heated at reflux with 1.2 g. of unsymmetrical dimethylhydrazine in 50 ml. of ethanol for 16 hours. The solution is cooled and filtered. Fractional crystallization of the solid separates the isomers 3-ethyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, dimethylhydrazone and 3-ethyl-6-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, dimethylhydrazone.

Example 3

A mixture of 2.5 g. of 3-ethyl-7(and 6)-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, prepared as in Example 1, and 100 ml. of 10% aqueous sodium hydroxide is warmed for three minutes. The sodium salt which is separated by filtration is heated at reflux with 2.5 ml. of ethyl chloroformate and 25 ml. of ethanol for 15 minutes. The volatile material is removed to give a mixture of isomers, 1-carbethoxy-3-ethyl-7(and 6)-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one. These ketones are heated at reflux for six hours with 0.4 g. of hydrazine in 50 ml. of ethanol. Filtration and fractional crystallization separates the hydrazones of 1-carbethoxy-3-ethyl-7-trifluoromethylpyrazolo[3,4-a]-inden-4(1H)-one and 1-carbethoxy-3-ethyl-6-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one.

In similar fashion, a mixture of 1.0 g. of the sodium salt prepared above and 1 ml. of methyl chloroformate in ether solution is refluxed for 20 minutes and the resulting ketones are treated with excess hydrazine to give 1-carbomethoxy-3-ethyl-7(and 6)-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone.

Example 4

A mixture of 3.5 g. of 2-p-methoxybenzoyl-5-trifluoromethyl-1,3-indandione (prepared by condensing dimethyl 4-trifluoromethylphthalate, made as in Example 1, with p-methoxyacetophenone) and 1.0 g. of hydrazine in 75 ml. of ethanol is heated at reflux for 48 hours. Cooling separates a mixture of 3-p-methoxyphenyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone and 3-p-methoxyphenyl-6-trifluoromethylpyrazolo[3,4-a]inden-

4(1H)-one, hydrazone. These isomers are separated by fractional crystallization from aqueous ethanol.

Example 5

A mixture of 26.2 g. of dimethyl 4-trifluoromethylphthalate, made as in Example 1, 13.4 g. of methyl benzyl ketone, 5.7 g. of sodium methoxide and 125 ml. of benzene is heated while removing methanol azeotropically. Working up as in Example 1 gives 2-phenylacetyl-5-trifluoromethyl-1,3-indandione.

The dione (3.3 g.) is heated at reflux with 0.5 g. of hydrazine hydrate in ethanol solution for eight hours. The solution is cooled and diluted with cold water. The resulting solid is a mixture of 3-benzyl-7(and 6)-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one.

A mixture of 3.3 g. of the above prepared ketones, 0.6 g. of hydrazine and 75 ml. of ethanol is heated at reflux for 36 hours to give 3-benzyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone and 3-benzyl-6-trifluoromethylpyrazolo[3,4 - a]inden-4(1H)-one, hydrazone which are separated by fractional crystallization from aqueous ethanol.

Example 6

A mixture of 13.1 g. of dimethyl 4-trifluoromethylphthalate, prepared as in Example 1, 7.7 g. of p-chloroacetophenone, 3.6 g. of sodium ethoxide and 150 ml. of benzene is reacted as in Example 1 to give 2-p-chlorobenzoyl-5-trifluoromethyl-1,3-indandione.

Eleven grams of the indandione and 1.7 g. of hydrazine hydrate are heated at reflux in ethanol for four hours. Quenching with cold water wives 3-p-chlorophenyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one and 3-p-chlorophenyl - 6 - trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one. These crude ketones are reacted with an excess of hydrazine to give the corresponding hydrazones which are separated by fractional crystallization from aqueous ethanol.

Example 7

Hydrazine (0.3 g.) and 2.9 g. of 2-(4-pentenoyl)-5-trifluoromethyl-1,3-indandione, which is prepared by sodium methoxide condensation of 5-hexen-2-one and dimethyl 4-trifluoromethylphthalate, are refluxed in ethanol for ten hours. Cooling, diluting with water and filtering gives a mixture of isomers 3-(3-butenyl)-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one and 3-(3-butenyl) - 6-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one.

These ketones (1.4 g.) and 0.4 g. of hydrazine are refluxed in ethanol for 48 hours to give a mixture of the corresponding hydrazones. Separation of these hydrazones is accomplished by fractional crystallization from ethanol.

Example 8

A mixture of 6.0 g. of 2-pivalyl-5-trifluoromethyl-1,3-indandione (made by condensing pinacolone and dimethyl 4-trifluoromethylphthalate) and 1.1 g. of hydrazine hydrate in 100 ml. of ethanol is refluxed for two hours. The solution is cooled and diluted with cold water. The resulting solid is a mixture of isomers, 3-t-butyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one and 3-t-butyl-6-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one.

A mixture of 2.9 g. of the above prepared indenones and 0.5 g. of hydrazine in 75 ml. of ethanol is heated at reflux for 24 hours to give the desired 4-hydrazones which are separated by fractional crystallization.

Example 9

A mixture of 3.0 g. of 2-isovaleroyl-5-trifluoromethyl-1,3-indandione, prepared by sodium methoxide condensation of dimethyl 4-trifluoromethylphthalate and methyl iso-butyl ketone, and 1.0 g. of hydrazine is heated at reflux in 60 ml. of ethanol for 72 hours to give a mixture of 3 - isobutyl - 7 - trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone and 3-isobutyl-6-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone which are separable by fractional crystallization from isopropanol.

Example 10

Dimethyl 4-trifluoromethylphthalate, made as in Example 1, is condensed with a molar equivalent of acetone in the presence of sodium methoxide in benzene solution to give 2-acetyl-5-trifluoromethyl-1,3-indandione.

A mixture of 5.0 g. of the dione, 1.0 g. of hydrazine hydrate and 100 ml. of ethanol is heated at reflux for eight hours. Quenching gives a solid which is a mixture of isomers, 3-methyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one and 3-methyl-6-trifluoromethylpyrazolo-[3,4-a]inden-4(1H)-one.

These ketones (2.5 g.) are heated at reflux with 0.5 g. of hydrazine in ethanol solution for 24 hours to give the corresponding 4-hydrazones which are separated by fractional crystallization from ethanol.

Example 11

Two grams of the mixture of isomers, 3-methyl-7(and 6)-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, made as in Example 10, is converted to the potassium salt by reaction with an equivalent amount of potassium hydride. The potassium salt is separated by filtration and then refluxed with 5 ml. of acetyl chloride in ether suspension to give, upon evaporation of the volatiles, 1-acetyl-3-methyl - 7(and 6)-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one. This mixture of ketones is heated at reflux in ethanol with 2.0 g. of hydrazine for 36 hours. Isolation of the solid by filtration and fractional crystallization gives 1-acetyl-3-methyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone and 1-acetyl-3-methyl-6-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone.

Example 12

The potassium salt of 3-methyl-7(and 6)-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, prepared as in Example 11, (1.0 g.) is refluxed with 2.5 ml. of benzyl chloride in 60 ml. of ethanol for 15 minutes. Evaporating the volatile material in vacuo and refluxing the residue with 1.5 g. of hydrazine in 50 ml. of ethanol gives 1 - benzyl-3-methyl-7-trifluoromethylpyrazolo[3,4 - a]inden-4(1H)-one, hydrazone and the corresponding 6-trifluoromethyl isomer.

Example 13

A mixture of 3.5 g. of 2-nonanoyl-5-trifluoromethyl-1,3-indandione, prepared by condensing dimethyl 4-trifluoromethylphthalate and methyl octyl ketone, and 1.5 g. of hydrazine is heated at reflux in 125 ml. of ethanol for 48 hours. Filtration of the solid and fractional crystallization separates 3-octyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone and the corresponding 6-trifluoromethyl isomer.

Example 14

A mixture of 3.0 g. of 2-senecioyl-5-trifluoromethyl-1,3-indandione, prepared by sodium methoxide condensation of dimethyl 4-trifluoromethylphthalate with mesityl oxide, and 0.6 g. of hydrazine hydrate in 100 ml. of methanol is refluxed for five hours to give, upon quenching with cold water, a mixture of 3-dimethylvinyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one and the corresponding 6-trifluoromethyl compound.

This mixture of ketones (1.5 g) is treated with 0.5 g. of methylhydrazine to give 3-dimethylvinyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, methylhydrazone and the corresponding 6-trifluoromethyl compound which are separated by fractional crystallization from ethanol.

Example 15

Condensation of dimethyl 4-trifluoromethylphthalate, made as in Example 1, with m-methylacetophenone as in

Example 1 gives 2-m-toluoyl-5-trifluoromethyl-1,3-indandione.

A mixture of 3.3 g. of the indandione, 1.2 g. of hydrazine and 75 ml. of ethanol is heated at reflux for 72 hours to give, upon filtration and fractional crystallization from ethanol, 3-m-tolyl-7-trifluoromethylpyrazolo-[3,4-a]inden-4(1H)-one, hydrazone and 3-m-tolyl-6-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone.

Example 16

A mixture of 3.3 g. of 2-p-aminobenzoyl-5-trifluoromethyl-1,3-indandione, prepared as in Example 1 by condensation of dimethyl 4-trifluoromethylphthalate and p-aminoacetophenone, and 1.2 g. of hydrazine in 100 ml. of ethanol is heated at reflux for 48 hours. The resulting solid is fractionally crystallized from ethanol to give 3 - p - aminophenyl - 7 - trifluoromethylpyrazolo[3,4 - a]-inden-4(1H)-one, hydrazone and 3-p-aminophenyl-6-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone.

Example 17

A mixture of 26.2 g. of dimethyl 4-trifluoromethylphthalate, made as in Example 1, 200 ml. of toluene, 5.7 g. of sodium methoxide and 8.4 g. of cyclopropyl methyl ketone is heated on a steam bath for ten hours. The mixture is concentrated in vacuo and the residue is dissolved in water. Acidifying the aqueous solution with hydrochloric acid and extracting with ether gives 2-cyclopropylcarbonyl-5-trifluoromethyl-1,3-indandione.

A mixture of 14.1 g. of the indandione, 2.5 g. of hydrazine hydrate and 150 ml. of ethanol is heated at reflux for six hours. Cooling, diluting with cold water and filtering gives a mixture of 3-cyclopropyl-7-trifluoromethylpyrazolo[3,4 - a]inden - 4(1H) - one and 3-cyclopropyl - 6 - trifluoromethylpyrazolo[3,4 - a]inden-4(1H)-one.

These indenones are refluxed with excess hydrazine in ethanol to give the corresponding 4-hydrazones which are separated by fractional crystallization from aqueous ethanol.

Example 18

A mixture of 2.8 g. of 3-cyclopropyl-7(and 6)-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, made as in Example 17, and 0.6 g. of unsymmetrical diethylhydrazine in 75 ml. of ethanol is heated at reflux for 24 hours to give a mixture of isomers, 3-cyclopropyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, diethylhydrazone and the corresponding 6-trifluoromethyl compound, which are separated by fractional crystallization from aqueous ethanol.

Example 19

Cyclobutyl methyl ketone (9.8 g.) is condensed with 26.2 g. of dimethyl 4-trifluoromethylphthalate as outlined in Example 17 to give 2-cyclobutylcarbonyl-5-trifluoromethyl-1,3-indandione.

A mixture of 3.0 g. of this indandione and 1.0 g. of hydrazine in 75 ml. of ethanol is refluxed for 48 hours to give 3-cyclobutyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone and 3-cyclobutyl-6-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone.

Example 20

A mixture of 3.1 g. of 2-cyclopentylcarbonyl-5-trifluoromethyl-1,3-indandione, prepared as in Example 17 by the sodium methoxide condensation of dimethyl 4-trifluoromethylphthalate (made as in Example 1) and cyclopentyl methyl ketone, and 0.35 g. of hydrazine are heated at reflux in 60 ml. of ethanol for six hours. Cooling, quenching with cold water and filtering gives the solid isomers, 3-cyclopentyl-7-trifluoromethylpyrazolo[3,4-a]-inden-4(1H)-one and the corresponding 6-trifluoromethyl isomer.

These ketones (3.0 g.) and 0.5 g. of hydrazine in 50 ml. of ethanol are refluxed for 36 hours. The solution is filtered and the solid is fractionally crystallized from ethanol to give 3-cyclopentyl-7-trifluoromethylpyrazolo-[3,4-a]inden-4(1H)-one, hydrazone and 3-cyclopentyl-6-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone.

Example 21

A mixture of 3.2 g. of 2-cyclohexylcarbonyl-5-trifluoromethyl-1,3-indandione, prepared by condensing dimethyl 4-trifluoromethylphthalate and cyclohexyl methyl ketone, and 1.2 g. of hydrazine in 60 ml. of ethanol is heated at reflux for 48 hours. Cooling, filtering and fractionally crystallizing the solid gives 3-cyclohexyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone and 3-cyclohexyl - 6 - trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone.

Example 22

A mixture of 2.8 g. of the isomers, 3-cyclopropyl-7-trifluoromethylpyrazolo[3,4 - a]inden - 4(1H) - one and 3-cyclopropyl - 6 - trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, made as in Example 17, and 1.5 g. of phenylhydrazine in 100 ml. of methanol is refluxed for 48 hours. Cooling yields a mixture of isomers which are separated by fractional crystallization from ethanol to give 3-cyclopropyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, phenylhydrazone and the corresponding 6-trifluoromethyl isomer.

Example 23

Dimethyl 4-trifluoromethylphthalate, prepared as in Example 1, is condensed with p-methoxyacetophenone as in Example 17 to give 2-p-methoxybenzoyl-5-trifluoromethyl-1,3-indandione.

This indandione (7.0 g.) and 1.0 g. of hydrazine hydrate are refluxed in ethanol for three hours. Cooling, adding cold water and filtering yields a mixture of isomers, 3-p-methoxyphenyl - 7 - trifluoromethylpyrazolo-[3,4-a]inden-4(1H)-one and 3-p-methoxyphenyl-6-trifluoromethylpyrazolo[3,4-a]inden - 4(1H) - one. Refluxing these ketones with excess hydrazine in ethanol solution gives the respective hydrazone derivatives which are separated by fractional crystallization from ethanol.

Example 24

Dimethyl 3-trifluoromethylphthalate (prepared from 2-amino-3-trifluoromethylbenzoic acid by diazotization and treatment with cuprous cyanide to give 2-cyano-3-trifluoromethylbenzoic acid, hydrolysis to give 3-trifluoromethylphthalic acid and esterification as described in Example 1) is condensed with an equivalent amount of methyl ethyl ketone in benzene solution containing sodium methoxide to give 2-propionyl-4-trifluoromethyl-1,3-indandione.

A mixture of 13.5 g. of the above prepared indandione, 2.5 g. of hydrazine hydrate and 125 ml. of ethanol is heated at reflux for six hours. Quenching with water gives the solid material, 3-ethyl-8-trifluoromethylpyrazolo-[3,4-a]inden-4(1H)-one and 3-ethyl-5-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one.

Treatment of these ketone isomers with 1.7 g. of hydrazine in ethanol solution gives the corresponding hydrazone derivatives which are separable by fractional crystallization from ethanol.

Example 25

Hydrazine (0.35 g.) and 3.1 g. of 2-(3-methylcyclobutyl)carbonyl-5-trifluoromethyl-1,3-indandione in 50 ml. of ethanol are refluxed for six hours. Quenching with cold water and filtering gives a mixture of 3-(3-methylcyclobutyl) - 7 - trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one and the corresponding 6-trifluoromethyl isomer.

Refluxing these ketones and 0.4 g. of hydrazine in ethanol solution, cooling and filtering gives the corresponding 4-hydrazone derivatives. Fractional crystallization separates 3-(3-methylcyclobutyl) - 7 - trifluoromethylpy-

razolo[3,4-a]inden-4(1H)-one, hydrazone and the corresponding 6-trifluoromethyl isomer.

Example 26

Hydrazine hydrate (2.1 g.) and 7.0 g. of 2-(2-ethyl-2-cyclohexen-1-yl)carbonyl - 5 - trifluoromethyl-1,3-indandione (prepared by condensing 2-ethyl-2-cyclohexen-1-yl methyl ketone with dimethyl 4-trifluoromethylphthalate) are heated at reflux for 48 hours in ethanol. Cooling and filtering yields a mixture of isomers 3-(2-ethyl-2-cyclohexen - 1 - yl)-7(and 6)-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone. Separation of these isomers is accomplished by fractional crystallization from aqueous ethanol.

Example 27

A solution of 1.5 g. of 3-cyclopropyl-7(and 6)trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, made as in Example 17, in 60 ml. of ether-tetrahydrofuran is refluxed with 0.3 g. of potassium amide for ten minutes. The potassium salt is filtered off and refluxed with 5.0 g. of methyl iodide in ethanol solution for four hours. The volatiles are removed to leave 3-cyclopropyl-1-methyl-7-trifluoromethylpyrazolo[3,4-a)inden-4(1H)-one and the corresponding 6-trifluoromethyl isomer. These ketones are refluxed with 0.5 g. of hydrazine in 100 ml. of methanol for 48 hours to give the 4-hydrazone derivatives. Separation of the isomers is accomplished by fractional crystallization from ethanol.

Similarly the potassium salt (1.0 g.) prepared above is reacted with 6 ml. of butyl bromide in ethanol to give, after evaporation of the volatiles, 1-butyl-3-cyclopropyl-7(and 6)-trifluoromethylpyrazolo[3,4 - a]inden - 4(1H)-one. Treatment of these ketones with excess hydrazine in ethanol and fractional crystallization of the solid material thus obtained gives 1-butyl-3-cyclopropyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone and 1-butyl-3-cyclopropyl - 6 - trifluoromethylpyrazolo(3,4-a]-inden-4(1H)-one. hydrazone.

Example 28

The potassium salt of 3-cyclopropyl-7(and 6)-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, prepared as in Example 27, (1.0 g.) is refluxed with 0.7 g. of benzenesulfonyl chloride in 25 ml. of ether for ten minutes. Evaporation of the reaction mixture leaves, as the residue, 1-benzenesulfonyl-3-cyclopropyl-7(and 6)-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one. This mixture of ketones is reacted with an excess of methylhydrazine in ethanol to give the corresponding 4-methylhydrazones which are separated by fractional crystallization from ethanol.

Example 29

A mixture of 3.2 g. of 2-benzoyl-4-trifluoromethyl-1,3-indandione, made by sodium methoxide condensation of dimethyl 3-trifluoromethylphthalate (prepared as in Example 24) and acetophenone, and 0.32 g. of hydrazine in 75 ml. of ethanol is refluxed for four hours to give, upon cooling and filtering 3-phenyl-8-trifluoromethylpyrazolo-[3,4-a]inden-4(1H)-one and 3-phenyl-5-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one.

These ketones are refluxed with 0.5 g. of hydrazine in ethanol solution to give the corresponding hydrazone derivatives which are separated by fractional crystallization from ethanol.

Example 30

A mixture of the isomers, 3-phenyl-8(and 5)-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one (made as in Example 29) (2.0 g.) and 100 ml. of 10% sodium hydroxide solution is warmed for three minutes. The sodium salt is separated by filtration and heated at reflux with 5 ml. of propionyl chloride in ethanol for 15 minutes. The volatiles are removed to give 3-phenyl-1-propionyl-8(and 5)-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one.

These ketones, 0.5 g. of hydrazine and 75 ml. of ethanol are refluxed for 16 hours. The solid material is filtered off and fractionally crystallized from ethanol to give 3-phenyl-1-propionyl-8-trifluoromethylpyrazolo [3,4-a]inden-4(1H)-one, hydrazone and the corresponding 5-trifluoromethyl isomer.

Example 31

A mixture of 2.8 g. of 2-isobutyryl-5-trifluoromethyl-1,3-indandione, prepared by condensation of methyl isopropyl ketone with dimethyl 4-trifluoromethylphthalate as in Example 1, and 0.5 g. of hydrazine hydrate in 75 ml. of ethanol is refluxed for four hours. Diluting with cold water gives 3-isopropyl-7-trifluoromethylpyrazolo-[3,4-a]inden-4(1H)-one and the corresponding 6-trifluoromethyl isomer.

Refluxing these ketones with 0.5 g. of hydrazine in ethanol solution for 36 hours gives the corresponding 4-hydrazones. Separation of these hydrazones is accomplished by fractional crystallization from ethanol.

Example 32

A mixture of 2.5 g. of 3-isopropyl-7(and 6)-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, made as in Example 31, and 100 ml. of 10% aqueous sodium hydroxide is warmed for five minutes. The sodium salt, isolated by concentrating and filtering the reaction mixture, is refluxed with 5 ml. of phenethyl chloride in ethanol to give, upon evaporation of the volatiles, 3-isopropyl-1-phenethyl - 7 - trifluoromethylpyrazolo[3,4 - a]inden-4-(1H)-one and the corresponding 6-trifluoromethyl isomer.

Reaction of the above prepared ketones with excess hydrazine furnishes a mixture of the corresponding hydrazones which are separated by fractional crystallization from ethanol.

Example 33

A mixture of 14.1 g. 2-cyclopropylcarbonyl-4-trifluoromethyl-1,3-indandione (made by condensing cyclopropyl methyl ketone with dimethyl 3-trifluoromethylphthalate as in Example 17), 1.6 g. of hydrazine and 200 ml. of ethanol is heated at reflux for six hours to give a mixture of 3-cyclopropyl-8-trifluoromethylpyrazolo[3,4-a]inden-4-(1H)-one and 3-cyclopropyl-5-trifluoromethylpyrazolo-[3,4-a]inden-4(1H)-one.

The corresponding hydrazones are prepared by refluxing these ketones with 2.0 g. of hydrazine in ethanol for 48 hours. Separation of the hydrazones is carried out by fractional crystallization from ethanol.

Example 34

A mixture of 2.8 g. of 3-cyclopropyl-8(and 5)-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one (made as in Example 33) and 0.7 g. of ethylhydrazine in 70 ml. of ethanol is heated at reflux for 24 hours to give a mixture of isomers, 3-cyclopropyl-8-trifluoromethylpyrazolo-[3,4-a]inden-4(1H)-one, ethylhydrazone and 3-cyclopropyl-5-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, ethylhydrazone.

Example 35

A mixture of 5.6 g. of 2-isobutyryl-4-trifluoromethyl-1,3-indandione, made by condensing methyl isopropyl ketone with dimethyl 3-trifluoromethylphthalate, and 1.5 g. of hydrazine are refluxed with 100 ml. of ethanol for 72 hours to give, upon cooling and filtering, a mixture of 3-isopropyl-8-trifluoromethylpyrazolo[3,4-a]inden-4-(1H)-one, hydrazone and 3-isopropyl-5-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone.

Example 36

A mixture of 3.0 g. of 5-trifluoromethyl-2-valeryl-1,3-indandione (prepared by condensation of 2-hexanone with dimethyl 4-trifluoromethylphthalate as in Example 1) and 0.5 g. of hydrazine hydrate is refluxed in ethanol for two hours. Cooling, adding cold water and filtering gives 3-n-butyl-7-trifluoromethylpyrazolo[3,4-a]inden-4-

(1H)-one and the corresponding 6-trifluoromethyl isomer.

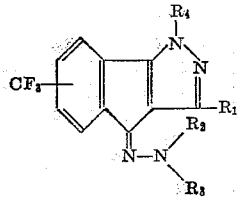
The above prepared ketones (2.9 g.) and 0.5 g. of hydrazine are refluxed for 20 hours in ethanol solution to give upon cooling and fractional crystallization from aqueous ethanol 3-n-butyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone and 3-n-butyl-6-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone

Example 37

A mixture of 0.6 g. of hydrazine and 2.9 g. of 2-(4-pentenoyl)-4-trifluoromethyl-1,3-indandione, made by condensation of 5-hexen-2-one and dimethyl 3-trifluoromethylphthalate as in Example 17, is refluxed for 48 hours in ethanol to give upon cooling and filtering a mixture of 3-(3-butenyl)-8-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone and 3-(3-butenyl)-5-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone which are separated by fractional crystallization from ethanol.

What is claimed is:

1. A chemical compound having the following formula:



in which R_1 is a member selected from the group consisting of alkyl having 1 to 8 carbon atoms inclusive, alkenyl having 2 to 8 carbon atoms inclusive, benzyl, phenethyl, phenyl, aminophenyl, halophenyl, lower alkylphenyl, lower alkoxyphenyl, cycloalkyl having 3 to 6 carbon atoms inclusive and cycloalkenyl having 4 to 6 carbon atoms inclusive; R_2 and R_3 are members selected from the group consisting of hydrogen, alkyl having 1 to 4 carbon atoms inclusive and, when taken together with the nitrogen atom to which they are attached, monophenylamino, and R_4 is a member selected from the group consisting of hydrogen, alkyl having 1 to 4 carbon atoms inclusive, benzyl, phenethyl, benzenesulfonyl, benzoyl, acetyl, propionyl, carbethoxy and carbomethoxy.

2. 3-isopropyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone.

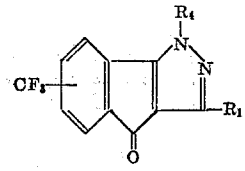
3. 3-isopropyl-6-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone.

4. 3-n-butyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone.

5. 3-(3-butenyl)-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone.

6. 3-cyclopropyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one, hydrazone.

7. A chemical compound having the following formula:



in which R_1 is a member selected from the group consisting of alkyl having 1 to 8 carbon atoms inclusive, alkenyl having 2 to 8 carbon atoms inclusive, benzyl, phenethyl, phenyl, aminophenyl, halophenyl, lower alkylphenyl, lower alkoxyphenyl, cycloalkyl having 3 to 6 carbon atoms inclusive, and cycloalkenyl having 4 to 6 carbon atoms inclusive; and R_4 is a member selected from the group consisting of hydrogen, alkyl having 1 to 4 carbon atoms inclusive, benzyl, phenethyl, benzenesulfonyl, benzoyl, acetyl, propionyl, carbethoxy and carbomethoxy.

8. 3-n-butyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one.

9. 3-isopropyl-6-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one.

10. 3-isopropyl-7-trifluoromethylpyrazolo[3,4-a]inden-4(1H)-one.

11. 3-cyclopropyl-7-trifluoromethylpyrazolo[3,4-a]-inden-4(1H)-one.

No references cited.