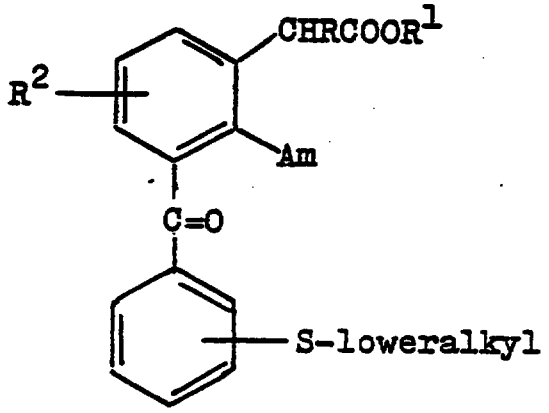
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# "7-(S-LOWERALKYLTHIOBENZOYL)INDOLIN-2-ONES"

The present invention relates to certain novel 7-(S-loweralkylthiobenzoyl)indolin-2-ones useful as intermediates in the preparation of 2-amino-3-benzoyl-phenylacetic acids having alkylthio substitution on the benzoyl moiety, their alkylesters and metal salts, which have pharmaceutical activity and which are described and claimed in our copending G.B. Application No. 80.22968 Serial No. 2055820 from which the present application is divided.

Such 2-amino-3-(alkylthiobenzoyl)phenylacetic acids, alkylesters and metal salts have the formula:




Formula I

wherein:

R represents a hydrogen atom or a lower alkyl group,

$R^1$ represents a hydrogen atom or a lower alkyl

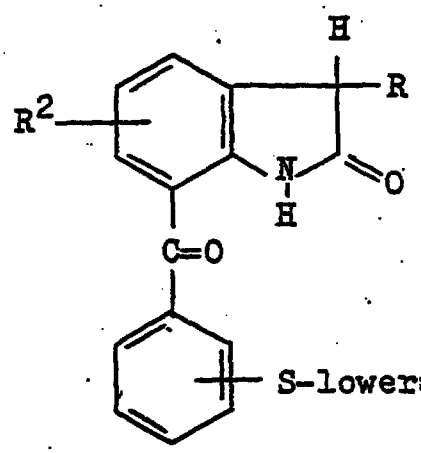
group or a pharmaceutically acceptable metal cation,

$R^2$ represents a hydrogen or a halogen atom or a lower alkyl or lower alkoxy group, and

Am represents a primary amino ($-NH_2$), methylamino or dimethylamino group.

The novel compounds of Formula I possess valuable pharmacological properties and are useful as pharmaceutical agents. The compounds exhibit anti-inflammatory and analgesic activity and inhibit blood platelet aggregation in warm-blooded animals.

The 7-(S-loweralkylthiobenzoyl)indolin-2-ones according to the present invention may be represented by Formula II:




Formula II

wherein R, $R^1$ and $R^2$ are as hereinabove defined.

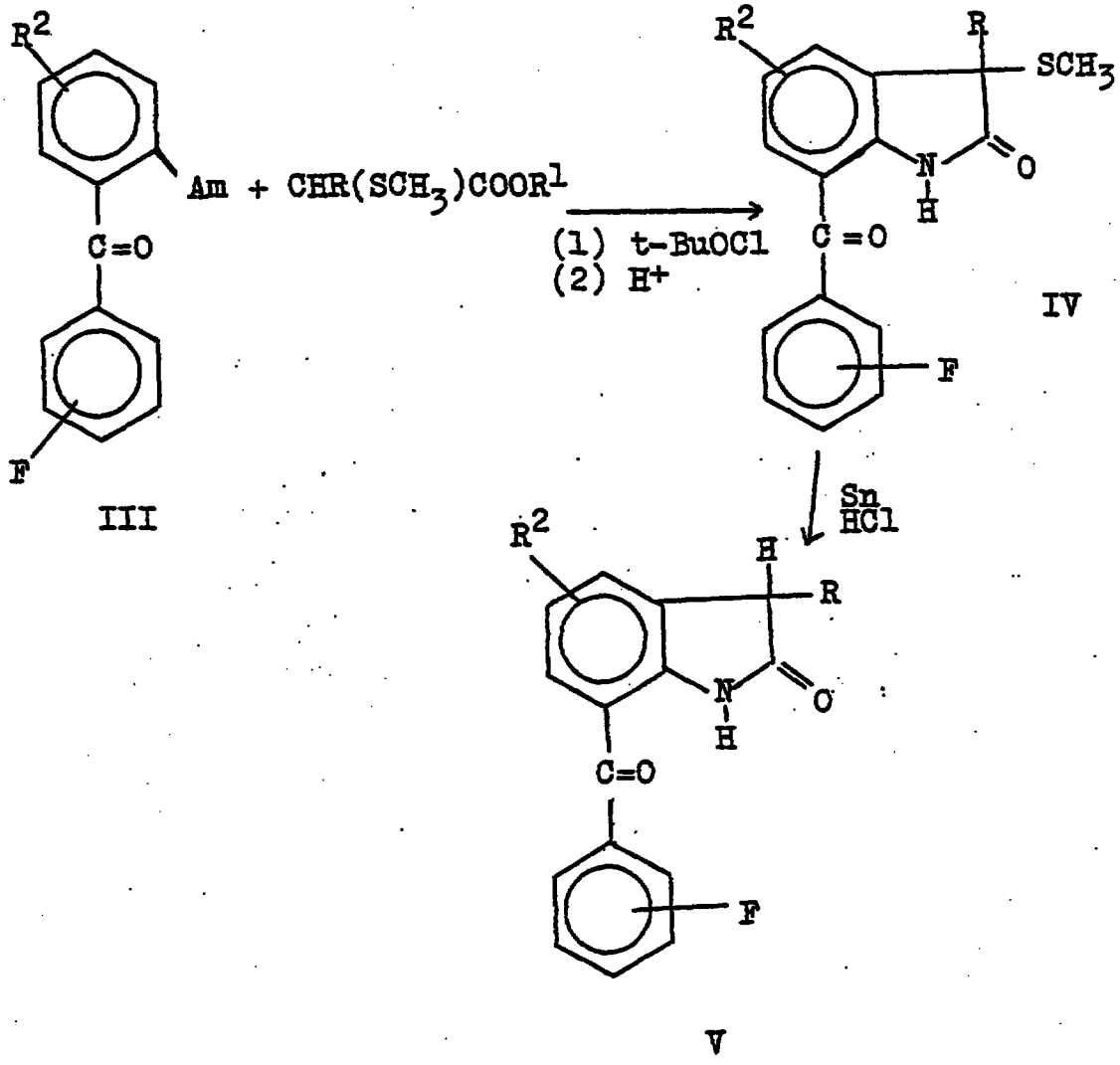
In the definition of the symbols of the formulae hereof and where they appear elsewhere throughout this specification, the terms have the following significance.

The term "lower alkyl" as used herein includes straight and branched chain groups of up to six carbons inclusive, and is exemplified by such groups as methyl, ethyl, propyl, isopropyl, butyl, secondary butyl, tertiary butyl, amyl, isoamyl and hexyl. Preferably lower alkyl groups having no more than four carbon atoms are used. The term "lower alkoxy" has the formula -O-lower alkyl.

The term "halogen" when referred to herein means Cl, F, Br and I.

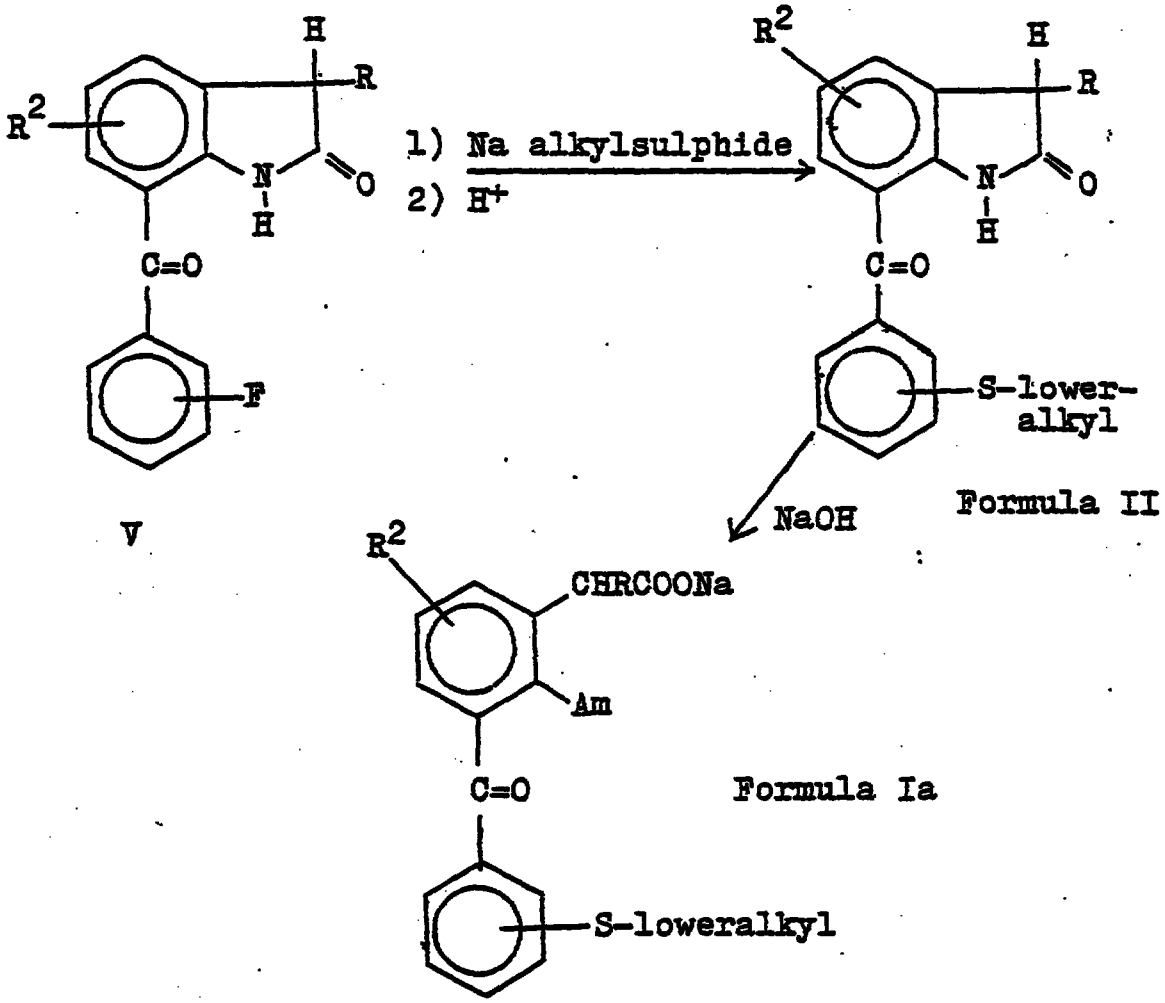
Illustrative of pharmaceutically acceptable metal cations are sodium, potassium, calcium, magnesium, zinc, copper and the hydrates thereof.

The starting fluorobenzoylindolin-2-ones used to prepare the compounds of this invention may be prepared by one or more of the methods disclosed in U.S. Patent 4,045,576. One method disclosed therein begins by reacting 2-amino-4'-halobenzoylbenzophenone with ethyl methylthioacetate, t-BuOCl (tertiary butyl oxychloride) and $Et_3N$ (triethylamine) to give 7-(halobenzoyl)-3-methylthioindolin-2-ones which are then reduced using a Raney nickel catalyst to produce the 7-(halobenzoyl)-3-indolin-2-one. A modification of this procedure was used wherein the Raney nickel was replaced by tin powder in alcohol and concentrated hydrochloric acid. The following equation is representative of the preparation of 7-(fluorobenzoyl)-indolin-2-ones used to prepare the compounds of the invention:




The preparation of the compounds of this invention is accomplished by reacting fluorobenzoyl indolin-2-ones with alkalimetal alkylsulphide, followed by acid hydrolysis to obtain the 7-(alkylthiobenzoyl)indolin-2-ones of the present invention. These may then be hydrolyzed with an alkali-metal base to give the alkali-metal salt of the 2-amino-3-(alkylthiobenzoyl)phenylacetic acids of the parent application. The following reaction sequence illustrates the _

preparation of the alkali-metal salts of the compounds of Formula I:




V

Formula II

Formula Ia

To obtain the free acid ($R^1$ = H) from the alkali metal salt, acetic acid is carefully added to an aqueous solution of the salt which causes the free acid to precipitate. The free acid is then separated by filtration, washed with water and dried. To obtain the ester

($R^1$ = lower alkyl), the alkali metal salt is treated in a suitable solvent such as dry dimethylformamide with a lower alkyl iodide. Water is added and the ester extracted from the mixture with a suitable solvent such as diethyl ether, dried over sodium sulphate and the solvent removed by evaporation.

The invention may be put into practice in various ways and a number of specific embodiments will be described to illustrate the invention with reference to the accompanying preparations 1 to 10 of starting materials, and Examples 1 to 4 of the compounds of the invention.

## Preparation 1

### 7-(4-Fluorobenzoyl)-3-methylthioindolin-2-one.

A solution of 42.2 g (0.196 mole) of 2-amino-4'-fluorobenzophenone in 2 litres of methylene chloride was cooled to -65°C and 26.5 g (0.198 mole) of ethyl methylthioacetate was added. A solution of 23.0 g (0.21 mole) of 95% tertiary butoxychloride in 50 ml of methylene chloride was added dropwise, keeping the temperature below -65°C. One hour after the addition was complete, 22.2 g (0.22 mol) of triethylamine was added dropwise and the mixture was allowed to warm to room temperature. The solution was concentrated to 700 ml and then washed with water. The organic solution was concentrated and the residue dissolved in 400 ml of methanol containing

30 ml of concentrated hydrochloric acid. The mixture was heated at reflux for one hour followed by cooling. The mixture was allowed to stand overnight, the crystals collected and washed with methanol to yield 31.4 g (53%) as bright yellow solid, m.p. 165-167.5°C.

Analysis: Calculated for $C_{16}H_{12}NO_2FS$: C, 63.77; H, 4.01; N, 4.65

Found : C, 63.58; H, 4.11; N, 4.67

Preparations 2A to 2G

Utilizing the procedure of Preparation 1 but substituting for 2-amino-4'-fluorobenzophenone, equal molar amounts of the following:

2-amino-4'-fluoro-4-methylbenzophenone,
2-amino-4'-fluoro-5-methylbenzophenone,
2-amino-4'-fluoro-6-methylbenzophenone,
2-amino-4'-fluoro-4-chlorobenzophenone,
2-amino-4'-fluoro-5-chlorobenzophenone,
2-amino-4'-fluoro-6-chlorobenzophenone,
2-amino-4'-fluoro-5-methoxybenzophenone,

there are obtained:

(2A) 7-(4-fluorobenzoyl)-4-methyl-3-methylthioindolin-2-one,

(2B) 7-(4-fluorobenzoyl)-5-methyl-3-methylthioindolin-2-one,

(2C) 7-(4-fluorobenzoyl)-6-methyl-3-methylthioindolin-2-one,

(2D) 7-(4-fluorobenzoyl)-4-chloro-3-methylthioindolin-2-one,

(2E) 7-(4-fluorobenzoyl)-5-chloro-3-methylthioindolin-2-one,

(2F) 7-(4-fluorobenzoyl)-6-chloro-3-methylthioindolin-2-one,

(2G) 7-(4-fluorobenzoyl)-5-methoxy-3-methylthio-indolin-2-one.

Preparation 3

7-(2-Fluorobenzoyl)-3-methylthioindolin-2-one.

A solution of 86 g (0.4 mole) of 2-amino-2'-fluorobenzophenone in 3 litres of methylene chloride was cooled to -65°C and 54 g (0.4 mole) of ethyl methylthio-acetate was added. A solution of 46 g (0.42 mole) of 95% tertiary butoxychloride in 100 ml of methylene chloride was added dropwise keeping the temperature below -65°C. One hour after the addition was complete, 41 g (0.4 mole) of triethylamine was added dropwise and the mixture allowed to warm up to room temperature. The solution was concentrated to about 1400 ml and then washed with water. The organic solution was concentrated and the residue dissolved in 800 ml methanol containing 60 ml of concentrated hydrochloric acid. The mixture was heated at reflux for one hr followed by cooling. The mixture stood overnight, then the crystals were collected and recrystallized from 20% aqueous ethanol to give 66 g (55%) pale yellow needles, m.p. 147.0-148.5°C.

Analysis: Calculated for $C_{16}H_{12}NO_2FS$: C, 63.77; H, 4.01; N, 4.65

Found : C, 63.97; H, 4.19; N, 4.66

Preparation 4

Utilizing the procedure of Preparation 3 but

substituting for 2-amino-2'-fluorobenzophenone, equal molar amounts of

2-amino-3'-fluorobenzophenone,

there is obtained:

7-(3-fluorobenzoyl)-3-methylthioindolin-2-one.

Preparation 5

7-(4-Fluorobenzoyl)indolin-2-one.

This is the starting material for Example 1.

A mixture of 40.0 g (0.133 mole) of 7-(4-fluorobenzoyl)-3-methylthioindolin-2-one and 40.0 g (0.34 mole) of tin powder in one litre of 95% ethanol was heated to reflux and 100 ml of concentrated hydrochloric acid was added. The mixture was heated for 6 hrs, then filtered while hot. The filtrate was cooled and the precipitate was collected and recrystallized from isopropyl alcohol to yield 24.5 g (72%) as off-white needles, m.p. 185-187.0°C.

Analysis: Calculated for $C_{15}H_{10}NO_2F$: C, 70.58; H, 3.95; N, 5.49

Found : C, 70.80; H, 4.12; N, 5.51

Preparations 6A to 6G

Utilizing the procedure of Preparation 5 but substituting for 7-(4-fluorobenzoyl)-3-methylthioindolin-2-one, equal molar amounts of the following:

7-(4-fluorobenzoyl)-4-methyl-3-methylthioindolin-2-one,

7-(4-fluorobenzoyl)-5-methyl-3-methylthioindolin-2-one,

7-(4-fluorobenzoyl)-6-methyl-3-methylthioindolin-2-one,

7-(4-fluorobenzoyl)-4-chloro-3-methylthioindolin-2-one,
7-(4-fluorobenzoyl)-5-chloro-3-methylthioindolin-2-one,
7-(4-fluorobenzoyl)-6-chloro-3-methylthioindolin-2-one,
7-(4-fluorobenzoyl)-5-methoxy-3-methylthio-indolin-2-one,

there are obtained:

(6A) 7-(4-fluorobenzoyl)-4-methylindolin-2-one,
(6B) 7-(4-fluorobenzoyl)-5-methylindolin-2-one,
(6C) 7-(4-fluorobenzoyl)-6-methylindolin-2-one,
(6D) 7-(4-fluorobenzoyl)-4-chloroindolin-2-one,
(6E) 7-(4-fluorobenzoyl)-5-chloroindolin-2-one,
(6F) 7-(4-fluorobenzoyl)-6-chloroindolin-2-one,
(6G) 7-(4-fluorobenzoyl)-5-methoxyindolin-2-one.

## Preparation 7

### 7-(2-Fluorobenzoyl)-indolin-2-one.

A mixture of 60 g (0.2 mole) of 7-(2-fluoro-benzoyl)-3-methylthioindolin-2-one and 60 g (0.5 mol) of tin powder in one litre of 95% ethanol was heated to reflux and 150 ml of concentrated hydrochloric acid was added. Heating was continued for 18 hrs then the mixture was cooled and the precipitate was collected by decanting the slurry from the remaining tin and filtering the slurry. The filter cake was recrystallized twice from absolute ethanol to give 31 g (60%) white needles, m.p. 209-210°C.

Analysis: Calculated for $C_{15}H_{10}NO_2F$: C, 70.58; H, 3.95; N, 5.49

Found : C, 70.31; H, 4.08; N, 5.56

Preparation 8

Utilizing the procedure of Preparation 7 but substituting for 7-(2-fluorobenzoyl)-3-methylthio-indolin-2-one, equal molar amounts of the following:

7-(3-fluorobenzoyl)-3-methylthioindolin-2-one,

there is obtained:

7-(3-fluorobenzoyl)-indolin-2-one.

Preparation 9

Utilizing the procedure of Preparation 1 but substituting equal molar amounts of ethyl α-(methylthio) propionate for ethyl methylthioacetate,

there is obtained

7-(4-fluorobenzoyl)-3-methyl-3-methylthioindolin-2-one.

Preparation 10

Utilizing the procedure of Preparation 5 but substituting equal molar amount of 7-(4-fluorobenzoyl)-3-methyl-3-methylthioindolin-2-one,

there is obtained

7-(4-fluorobenzoyl)-3-methylindolin-2-one.

The reaction conditions employed for preparing the novel intermediates and compounds of the invention are more fully illustrated in the examples which follow.

Example 1

7-(4-Methylthiobenzoyl)indolin-2-one.

($R^2$=R=H; lower alkyl =$CH_3$)

A solution of sodium methyl mercaptide, prepared from 400 ml of 3N sodium hydroxide and 24 g (0.5 mole) of methyl sulphide, was mixed with 25.5 g (0.1 mole) of 7-(4-fluorobenzoyl)indolin-2-one (see Preparation 5).

The mixture was refluxed for 1.5 hr, cooled and acidified with caution since much methyl sulphide evolves rapidly. The resulting precipitate was collected and recrystallized twice from benzene to give 17.8 g (70%) as yellow crystals, m.p. 167.0-169.0°C.

Analysis: Calculated for $C_{16}H_{13}NO_2S$: C, 67.82; H, 4.63; N, 4.94

Found : C, 67.65; H, 4.63; N, 4.91

Examples 2A to 2I

Utilizing the procedure of Example 1 but substituting for 7-(4-fluorobenzoyl)indolin-2-one, equal molar amounts of the following:

7-(4-fluorobenzoyl)-4-methylindolin-2-one, (see Preparation 6A)

7-(4-fluorobenzoyl)-5-methylindolin-2-one, (see Preparation 6B)

7-(4-fluorobenzoyl)-6-methylindolin-2-one, (see Preparation 6C)

7-(4-fluorobenzoyl)-4-chloroindolin-2-one, (see Preparation 6D)

7-(4-fluorobenzoyl)-5-chloroindolin-2-one, (see Preparation 6E)

7-(4-fluorobenzoyl)-6-chloroindolin-2-one, (see Preparation 6F)

7-(4-fluorobenzoyl)-5-methoxyindolin-2-one, (see Preparation 6G)

7-(2-fluorobenzoyl)-indolin-2-one, (see Preparation 7)

7-(3-fluorobenzoyl)indolin-2-one, (see Preparation 8)

there are obtained:

7-(4-methylthiobenzoyl)-4-methylindolin-2-one, (Example 2A)

7-(4-methylthiobenzoyl)-5-methylindolin-2-one, (Example 2B)

7-(4-methylthiobenzoyl)-6-methylindolin-2-one, (Example 2C)

7-(4-methylthiobenzoyl)-4-chloroindolin-2-one, (Example 2D)

7-(4-methylthiobenzoyl)-5-chloroindolin-2-one, (Example 2E)

7-(4-methylthiobenzoyl)-6-chloroindolin-2-one, (Example 2F)

7-(4-methylthiobenzoyl)-5-methoxyindolin-2-one, (Example 2G)

7-(2-methylthiobenzoyl)indolin-2-one (Example 2H).

7-(3-methylthiobenzoyl)indolin-2-one (Example 2I).

Examples 3A to 3C

Utilizing the procedure of Example 1 but substituting for sodium methyl mercaptide, equal molar amounts of the following:

sodium ethylmercaptide,

sodium isopropylmercaptide,

sodium-n-butylmercaptide,

there are obtained the following:

7-(4-ethylthiobenzoyl)indolin-2-one, (Example 3A)

7-(4-isopropylthiobenzoyl)indolin-2-one, (Example 3B)

7-(4-n-butylthiobenzoyl)indolin-2-one (Example 3C).

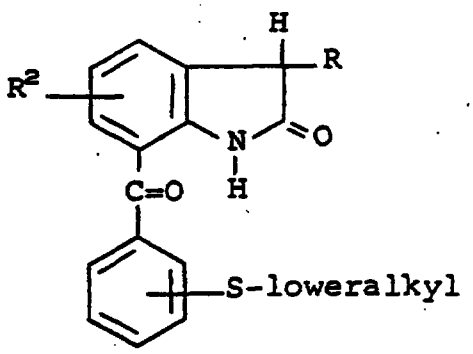
EXAMPLE 4

7-(4-Methylthiobenzoyl)-3-methylindolin-2-one.

Utilizing the procedure of Example 1 but substituting 7-(4-fluorobenzoyl)-3-methylindolin-2-one (see Preparation 10) for 7-(4-fluorobenzoyl)indolin-2-one, the titled compound is obtained.

## CLAIMS

1. 7-(S-loweralkylthiobenzoyl)indolin-2-ones having the formula




wherein;

R represents a hydrogen atom or a lower alkyl group, and

$R^2$ represents a hydrogen or a halogen atom or a lower alkyl or lower alkoxy group.

2. 7-(4-Methylthiobenzoyl) indolin-2-one.

3. 7-(4-Methylthiobenzoyl)-4-methylindolin-2-one.

4. 7-(4-Methylthiobenzoyl)-5-methylindolin-2-one.

5. 7-(4-Methylthiobenzoyl)-6-methylindolin-2-one.

6. 7-(4-Methylthiobenzoyl)-4-chloroindolin-2-one.

7. 7-(4-Methylthiobenzoyl)-5-chloroindolin-2-one.

8. 7-(4-Methylthiobenzoyl)-6-chloroindolin-2-one.

9. 7-(4-Methylthiobenzoyl)-5-methoxyindolin-2-one.

10. 7-(2-Methylthiobenzoyl) indolin-2-one.

11. 7-(3-Methylthiobenzoyl) indolin-2-one.

12. 7-(4-Ethylthiobenzoyl) indolin-2-one.

13. 7-(4-Isopropylthiobenzoyl)indolin-2-one.

14. 7-(4-n-Butylthiobenzoyl) indolin-2-one.

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