COMMONWEALTH OF AUSTRALIA

502,015

PATENTS ACT 1952-1969

CONVENTION APPLICATION FOR A PATENT

(This form may be signed by the applicant or by the Australian Patent Attorney)

Insert full name(s) and address(es) of applicant(s)

LILLY INDUSTRIES LIMITED, of Henrietta House, Henrietta Place, London W.1., England,

hereby apply for the grant of a Patent for an invention entitled

"KETONE DERIVATIVES"

which is described in the accompanying complete specification. The application is a Convention application and is based on the application(s) for patent or similar protection made in GREAT BRITAIN on 17th April, 1975 under No. 15805/75

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 18/5/19

My address for service is care of DAVIES & COLLISON, Patent Attorneys, of Cromwell Building, 374 Bourke Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

Dated this 15th day of April, 1976

(a) Signature(s) of applicant(s).

(b) Seal of Company (if any).

Note: Initial all Alterations.
COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1945-1960

DECLARATION IN SUPPORT OF CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

(The declaration shall be made by the applicant, or, if the applicant is a body corporate, by a person authorized by the body corporate to make the declaration on its behalf).

In support of the Application made for a patent for an invention entitled

KETONE DERIVATIVES

I, KENNETH WILLIAM HENRY McVEY, of Erl Wood Manor, Windlesham, Surrey, England,

1 3 1 5 4 / 7 6

do solemnly and sincerely declare as follows:—

1. (a) I am the applicant for the patent for the invention of

or (b) I am authorized by

LILLY INDUSTRIES LIMITED

the applicant........ for the patent........ for the invention to make this declaration on their behalf.

2. (a) I am the actual inventor of the invention:

or (b) JOHN CHRISTOPHER SAUNDERS, a British subject, of 4 Cookham Lodge, Courtlands, Maidenhead, Berkshire, England; and WILLIAM ROBERT NIGEL WILLIAMSON, a British subject, of "Littlecote" One Pin Lane, Farnham Common, Slough, Buckinghamshire, England, are the actual inventors........ of the invention and the facts upon which the applicant........ are entitled to make the application are as follows:—

By an Assignment dated 11th March 1976, whereby the said inventors assigned the invention to the said applicant

(Paragraphs 3 and 4 apply only to Convention applications).

3. The basic application........ as defined by Section 141 of the Act was made

in............ GREAT BRITAIN on the 17th April 1975

by............ LILLY INDUSTRIES LIMITED, of Henrietta House, Henrietta

Xrn.................................. on the Place, London W.1,

by........................................

4. The basic application........ referred to in paragraph 3 of this Declaration was made in a Convention country in respect of the invention the subject of the application.

Declared at Windlesham, this 11th day of March 1976.

LILLY INDUSTRIES LIMITED

Signature(s) of declarant(s).
CLAIM 1. A pharmaceutical formulation containing an active ingredient in association with a pharmaceutically acceptable carrier therefor, said active ingredient being a compound of the formula:

```
  R1
  |
  |
  |
  |
  |
  |
  R2
  |
  |
  |
  |
  |
  |
  R3
  |
  |
  |
  |
  |
  |
  C  --  Ar
  |
  Y
```

wherein \( R^2 \) is hydrogen or ethyl, \( R^1 \) and \( R^3 \) represent hydrogen, methyl or ethyl, at least one of \( R^1, R^2 \) and \( R^3 \) not being hydrogen; \( Ar \) is a phenyl group optionally substituted from one to three groups selected from chlorine, fluorine, methyl, carboxy, \( COO\) and trifluoromethyl; \( Z \) is hydrogen or \( COR^5 \); and \( Y \) is \( O, NOH \) or \( NOCOR^5 \), \( R^5 \) being \( C_{1-4} \) alkyl or phenyl, provided that

1. when \( Ar \) is 4-chlorophenyl, \( Y \) and \( Z \) are as defined above and \( R^1 \) and \( R^2 \) are hydrogen, \( R^3 \) is methyl;
(ii) when Ar is unsubstituted phenyl, Z is as defined above, R^1 and R^2 are hydrogen and R^3 is ethyl, Y is 0;
(iii) when R^1 is ethyl, R^2 and R^3 are hydrogen and Y and Z are as defined above, Ar is not 2,4- or 3,4-dichlorophenyl, 2- or 3-chlorophenyl or 4-fluorophenyl;
COMMONWEALTH of AUSTRALIA
PATENTS ACT 1952-1969

COMPLETE SPECIFICATION
(Original)

FOR OFFICE USE: 502,015

Application Number: 13154/76

Name of Applicant: LILLY INDUSTRIES LIMITED

Address of Applicant: Henrietta House, Henrietta Place, London W.1., England,

Actual Inventor(s): JOHN CHRISTOPHER SAUNDERS and WILLIAM ROBERT NIGEL WILLIAMSON

Address for Service: DAVIES & COLLISON, Patent Attorneys, Cromwell Building, 374 Bourke Street, Melbourne, 3000

Complete Specification for the invention entitled:

"KETONE DERIVATIVES"

The following statement is a full description of this invention, including the best method of performing it known to us:-
This invention relates to pharmaceutical formulations containing ω-hydroxybenzophenone derivatives.

There is a wealth of literature concerning the benzophenones, their preparation and their uses. However, it has not heretofore been appreciated that ω-hydroxybenzophenones, and derivatives thereof, can be used in the treatment of allergic conditions.

According to the present invention therefore, there is provided a pharmaceutical formulation containing an active ingredient in association with a pharmaceutically acceptable carrier therefor, said active ingredient being a compound of the formula:

\[
R^1\quad R^2C\quad \text{Ar}\quad Z\quad Y
\]

wherein \( R^2 \) is hydrogen or ethyl, \( R^1 \) and \( R^3 \) represent hydrogen, methyl or ethyl, at least one of \( R^1, R^2 \) and \( R^3 \) not being hydrogen; \( \text{Ar} \) is a phenyl group optionally substituted by from one to three groups selected from chlorine, fluorine, methyl, carboxy, \( \text{COOR}^5 \) and trifluoromethyl; \( Z \) is hydrogen or \( \text{COR}^5 \) and \( Y \) is \( 0, \text{NOH or NOCOR}^5, \text{R}^5 \) being \( \text{C}_{1-4} \) alkyl or phenyl, provided that

(i) when \( \text{Ar} \) is 4-chlorophenyl, \( Y \) and \( Z \) are as defined above and \( R^1 \) and \( R^2 \) are hydrogen, \( R^3 \) is methyl;

(ii) when \( \text{Ar} \) is unsubstituted phenyl, \( Z \) is as defined above, \( R^1 \) and \( R^2 \) are hydrogen and \( R^3 \) is ethyl, \( Y \) is 0;

(iii) when \( R^1 \) is ethyl, \( R^2 \) and \( R^3 \) are hydrogen and \( Y \) and \( Z \) are as defined above, \( \text{Ar} \) is not 2,4- or 3,4-dichlorophenyl, 2- or 3-chlorophenyl or 4-fluorophenyl.
In a further aspect of the invention, there is provided a method of treating a mammal suffering from an allergic condition, and particularly a method of treating immediate hypersensitivity diseases such as asthma in animals, including humans, which comprises administering to said mammal an anti-allergically effective dose of a compound of formula (I) as defined above.

In the formulation and method aspects of the present invention, a preferred sub-genus of the compounds of formula (I) are those wherein R¹, R² and R³ are as defined above, Ar is a phenyl group optionally substituted by from one to three groups selected from chlorine, fluorine or methyl, Z is hydrogen or COR⁵ and Y is O, NOH or NOCOR⁵, R⁵ being as defined above. Advantageously, the compound of formula (I) is one wherein one of R¹, R² and R³ is ethyl and the others are hydrogen; Ar is phenyl, 4-chlorophenyl, 4-fluorophenyl or 4-methylphenyl; Z is hydrogen; and Y is 0 and, within the latter group, a preferred sub-class are those compounds of formula (I) wherein Z is hydrogen; Y is 0 and either

(i) R¹ is ethyl, R² and R³ are hydrogen and Ar is 4-chlorophenyl;
(ii) R³ is ethyl, R¹ and R² are hydrogen and Ar is 2,4-dichlorophenyl; or
(iii) R² is ethyl, R¹ and R³ are hydrogen and Ar is 3- or 4-fluorophenyl.

As well as the above particularly preferred groups of compounds of the present invention, it has been found that the compounds of formula (I) likely to possess the most useful therapeutic index, i.e. combination of efficacy and lack of toxicity, are those having one or more of the following features:

(a) Z is hydrogen.
(b) Y is 0.
(c) one of R¹, R² and R³ is ethyl, the other R¹, R², R³ substituents being hydrogen.
(d) R¹ is ethyl when R² and R³ are hydrogen.
(e) Ar is a 4-chlorophenyl group.
(f) Ar is a 4-fluorophenyl group.
(g) Ar is unsubstituted phenyl.

Compounds in which Y is not O can exist in both syn and anti forms and it is to be understood that both of these isomers, and mixtures thereof, are included within the scope of the invention.

The preferred compound of the invention is 4'-chloro-5-ethyl-2-
The compounds of formula (I) useful in the formulations of the invention can be prepared by reacting a carboxylic acid of the formula A-COOH or a derivative thereof wherein A is selected from the groups or Ar-, under Friedel-Crafts' acylating conditions with a substituted benzene of formula B-H wherein B is selected from the same groups as A but is different therefrom to produce a compound of formula (I) in which Y is 0 and thereafter, if desired, reacting the resultant product with hydroxylamine in the presence of a base to produce the corresponding oxime in which Y is NOH, a compound in which Z is COR and/or Y is NOCOR being then obtained by acylation of the aforementioned compounds in which Z is hydrogen and/or Y is NOH.

Illustrative of a Friedel-Crafts' acylation as described above is the reaction between a compound of formula ArCOX and a compound of formula Z', being hydrogen or a protecting group such as methyl.

The reaction may be represented by the following reaction scheme:
wherein X is a halogen atom or hydroxyl.

When X is halogen, the reaction may be carried out using a Lewis acid such as an aluminium halide (e.g. the chloride) as catalyst in a suitable inert solvent such as 1,1,2,2-tetrachloroethane or carbon disulphide.

When X is hydroxyl, boron trifluoride or (CF₃CO)₂O are preferred catalysts, used with or without a suitable solvent.

If Z' is a protecting group, it may be removed in situ or subsequently, should it be desired to form a compound of formula (I) in which Z' is hydrogen.

Reduction of unwanted isomer(s) can be achieved by suitable choice of reaction conditions, temperature control being especially important. Ideally the reaction temperature is from 20°C to the reflux temperature and preferably from 80°C up to reflux temperature.

Similarly, the benzophenones can be prepared by the following reaction scheme:

\[
\begin{align*}
\text{R}_1 \quad & \quad \quad \quad \text{COX} + \text{HAr} \quad \rightarrow \quad \text{R}_1 \\
\text{R}_2 \quad & \quad \quad \quad \text{C} \quad \quad \text{Ar} \\
\end{align*}
\]

similar reaction conditions being applicable.

In the case of the reaction with a compound of the formula ArCOX, an initial reaction product (A) below may be obtained and isolated. This may be subjected to a Fries rearrangement using similar catalytic conditions:

\[
\begin{align*}
\text{A} \quad \rightarrow \quad \text{I} \\
\end{align*}
\]
as those described above, for example using aluminium chloride.

A further example of the acylation involving a derivative of A-COOH is the use of the compound Ar-CN as acylating agent. This modified process is known as the Houben-Hoesch Reaction which proceeds as shown below:

\[
\text{ArCN} + \text{Lewis acid} \rightarrow \text{ArCN} + \text{Ar-CN} \equiv \text{Ar-COOH}
\]

Where a protected hydroxy group Z' is used in the foregoing reactions, it may be converted to the desired hydroxy group by cleavage with, for example, HBr, BF₃, AlCl₃ or HI.

As outlined above, preparation of ketonic derivatives such as the oxime can be effected by combining a solution of the ketone, for example, an aqueous or alcoholic solution, with a derivative, preferably the hydrochloride, of hydroxylamine in the presence of a base, for instance sodium or potassium hydroxide.

Also, as stated above, preparation of the acyl derivatives of the \( \alpha \)-hydroxy or oxime groups can be carried out by a variety of methods, for example, by treating the \( \alpha \)-hydroxybenzophenone or oxime in a basic solution (e.g. pyridine or an aqueous solution of a group IA hydroxide such as sodium or potassium hydroxide) with an acid anhydride or halide (preferably the chloride) or with a solution of the acylating acid in the presence of the acid anhydride with a trace of catalyst (e.g. perchloric acid - 70%), or by refluxing the \( \alpha \)-hydroxybenzophenone or oxime with the acylating acid.

The \( \alpha \)-hydroxybenzophenones and derivatives thereof of the present invention have been shown to possess activity in one or more of the four tests regularly used to detect anti-allergy activity. Two of said tests are *in vitro* tests - the guinea pig and human chopped lung tests - and involve the direct measurement of the mediators, histamine and slow reacting
substance in anaphylaxis (SRS-A), shown to be released by asthmatic human lung. For compounds of the type comprising the present invention, a compound is considered to be active if at least 30% inhibition of SRS-A release in the guinea pig chopped lung test is achieved at a dose of 10 μg/ml or less. Depending on absorption, distribution and metabolism of the drug under test, activity in the chopped lung test at this level indicates in vivo dosage ranging from 0.5 to about 100 mg/Kg orally.

The other two tests are in vivo tests - the Herxheimer and rat peritoneal anaphylaxis - and reflect oral activity in two different species. In the Herxheimer test, sensitised guinea pigs are protected against the bronchospasm induced by an aerosol of antigen whilst, in the rat peritoneal anaphylaxis test, the SRS-A released on challenge is measured directly. Where an active compound is tested in these in vivo tests, activity at doses of 300 mg/Kg or less is normally achieved.

The compounds of the present invention display activity in one or more of the foregoing tests (the broadest spectrum compounds being those which display anti-allergy activity in all four tests) and are therefore useful in the prophylactic and therapeutic treatment of immediate hypersensitivity diseases including asthma and in the alleviation of status asthmaticus. In certain cases the compounds have been found to be useful in diseases in which excessive amounts of prostaglandins are released and as a respiratory stimulant. The compounds have low toxicity.

The compounds or compositions of the present invention may be administered by various routes and for this purpose may be formulated in a variety of forms. Thus the compounds or compositions may be administered by the oral and rectal routes, topically, parenterally, e.g. by injection and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sub-lingual tablets, sachets, cachets, elixirs, suspensions, aerosols, ointments, for example, containing from 1 to 10% by weight of the active compound in a suitable base, soft and
hard gelatin capsules, suppositories, injection solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injection solutions. Advantageously for this purpose, compositions may be provided in dosage unit form, preferably each dosage unit containing from 5 to 500 mg. (from 5.0 to 50 mg. in the case of parenteral administration, from 5.0 to 50 mg. in the case of inhalation and from 25 to 500 mg. in the case of oral or rectal administration) of a compound of formula (I).

As indicated by the tests referred to above, dosages of from 0.5 to 300 mg/kg per day, preferably 0.5 to 20 mg/kg, of active ingredient may be administered. It will however readily be understood that the amount of the compound or compounds of formula (I) actually to be administered will be determined by a physician, in the light of all the relevant circumstances including the condition to be treated, the choice of compound to be administered and the choice of route of administration and therefore the above preferred dosage range is not intended to limit the scope of the present invention in any way.

In this specification, the expression "dosage unit form" is used as meaning a physically discrete unit containing an individual quantity of the active ingredient, generally in admixture with a pharmaceutical diluent therefor, or otherwise in association with a pharmaceutical carrier, the quantity of the active ingredient being such that one or more units are normally required for a single therapeutic administration or that, in the case of severable units such as scored tablets, at least one fraction such as a half or a quarter of a severable unit is required for a single therapeutic administration.

The formulations of the present invention normally will consist of at least one compound of formula (I) associated with a pharmaceutically acceptable carrier therefor, i.e. mixed with a carrier, or diluted by a carrier, or enclosed or encapsulated by an ingestible carrier in the form of a capsule,
sachet, cachet, paper or other container or by a disposable container such as an ampoule. A carrier or diluent may be a solid, semi-solid or liquid material, which serves as a vehicle, excipient or medium for the active therapeutic substance.

Some examples of the diluents or carriers which may be employed in the pharmaceutical compositions of the present invention are lactose, dextrose, sucrose, sorbitol, mannitol, propylene glycol, liquid paraffin, white soft paraffin, kaolin, fumed silicon dioxide, microcrystalline cellulose, calcium silicate, silica, polyvinylpyrrolidone, cetostearyl alcohol, starch, modified starches, gum acacia, calcium phosphate, cocoa butter, ethoxylated esters, oil of theobroma, arachis oil, alginates, tragacanth, gelatin, syrup B.P., methyl cellulose, polyoxyethylene sorbitan monolaurate, ethyl lactate, methyl and propyl hydroxybenzoate, sorbitan trioleate, sorbitan sesquioleate and oleyl alcohol and propellants such as trichloromonofluoromethane, dichlorodifluoromethane and dichlorotetrafluoroethane. In the case of tablets, a lubricant may be incorporated to prevent sticking and binding of the powdered ingredients in the dies and on the punch of the tabletting machine. For such purpose there may be employed for instance aluminium, magnesium or calcium stearates, talc or mineral oil.
The following Examples illustrate how compounds of use in the formulations of the invention may be prepared:

**EXAMPLE 1**

2-Hydroxy-5-Methyl-4'-Chlorobenzophenone Oxime (syn and anti).

(a) 2-Hydroxy-5-methyl-4'-chlorobenzophenone (13.5 g, 0.055 moles) was stirred with a solution of potassium hydroxide (44 g) in water (150 ml.) and then hydroxylamine hydrochloride (17.4 g, 0.25 mole) was added with ice cooling. After stirring overnight at room temperature 100 ml. of water was added and the mixture was acidified with 5N-hydrochloric acid to give an off-white precipitate which was filtered, washed and dried (14.7 g).

Recrystallisation of the product from benzene gave 2-hydroxy-5-methyl-4'-chlorobenzophenone oxime (7 g, m.p. 163°C. (This was the stereoisomer in which the oxime -OH group and the 4'-chlorophenyl group were in the syn position relative to each other).

(b) The above procedure was repeated this time using 192 g (0.78 mole) of the benzophenone used in (a). The benzene solution deposited a second and third crop of crystals. The second crop (31.5 g) was a mixture of the two forms of the oxime whereas the third crop (1.9 g) was the stereoisomer in which the oxime hydroxyl group and the 4'-chlorophenyl group were in the anti-position relative to each other. (m.p. of product was 145-70°C).

The C,H,N,Cl microanalysis for each isomer was satisfactory.

(c) 4'-Chloro-2-hydroxy-5-methyl-benzophenone-oxime diacetate.

The oxime produced in (a) above (26.2 g) was dissolved in warm acetic anhydride (50 ml.), and on cooling a solid separated. This was filtered off and the filtrate evaporated to dryness, leaving a residue which was crystallised from ethanol to give the diacetate as the second crop. (m.p. 136°C.)
EXAMPLE 2

4'-Chloro-5-ethyl-2-hydroxybenzophenone

Aluminium chloride (267 g) was added in portions over 30 minutes to a stirred solution of 4-ethylphenol (122.1 g.) and 4-chlorobenzyol chloride (140 ml.) in dry 1,1,2,2-tetrachloroethane (800 ml.). The mixture was heated at 105°C. for 22 hours with stirring, and on cooling a mixture of ice (600 g) and concentrated hydrochloric acid was added slowly. A vigorous reaction occurred and some material was lost. The remaining material was separated, the aqueous fraction extracted twice with chloroform (200 ml.), and the combined organic layers evaporated to a dark oil which was distilled in vacuo giving two main fractions: B (17.4 g) 150-160°C @ 0.3 mmHg; C (110.8 g) 160-168°C. @ 0.3 mmHg.

The title compound was crystallised by cooling to -20°C. and recrystallised from n-hexane at 0°C. to give a yellow crystalline solid m.p. 35-8°C.

Microanalysis: C_{15}H_{13}ClO_2 requires 69.1%C, 5.0%H, 13.6%C; found 69.0%C, 5.0%H, 13.9%C.

EXAMPLE 3

4'-Chloro-5-ethyl-2-hydroxybenzophenone-oxime

4'-Chloro-5-ethyl-2-hydroxybenzophenone (65.2 g) and potassium hydroxide (170 g) in water (700 ml) and ethanol (150 ml.) were treated with hydroxylamine hydrochloride (70.0 g), with cooling, and the resulting mixture was stirred for 18 hours at ambient temperature. Dissolution occurred during this time. The solution was acidified with 5N-hydrochloric acid and then extracted with ether (3 x 200 ml.). The combined ether solutions were washed with 10% aqueous sodium carbonate solution (2 x 200 ml.) and evaporated to dryness to give an off-white solid. This solid was recrystallised from 40% benzene / 60-80°C petrol ether to give a white crystalline solid (29.9 g), second crop (14.5 g) m.p. 117°C.
**EXAMPLE 4**

2-Hydroxy-3-methyl-4'-chlorobenzophenone

Chlorobenzene (78.79 g, 71.6 ml; 0.7 mole) and AlCl₃ (14 g, 0.105 mole) were mixed, stirred and treated with a solution of 2-hydroxy-3-methylbenzoic acid chloride (12 g, 0.07 mole) in chlorobenzene (20 ml). The mixture was stirred and heated at 100°C overnight. The cooled mixture was added to conc. HCl (10 ml) and ice, extracted with ether, and ether washed with saturated sodium bicarbonate solution, dried (Na₂SO₄), filtered and the filtrate distilled, to give (after removal of the ether), a main fraction 2-hydroxy-3-methyl-4'-chlorobenzophenone, b.p. 148-152°C/0.5 mmHg (8.18 g), which solidified to yellow microplates, m.p. 55-58°C.

<table>
<thead>
<tr>
<th>Found</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>68.23</td>
</tr>
<tr>
<td>H</td>
<td>4.71</td>
</tr>
<tr>
<td>Cl</td>
<td>14.61</td>
</tr>
</tbody>
</table>

\[
\text{C}_{13}\text{H}_{14}\text{ClO}_2 \text{ requires: } C.68.16; H.4.49; Cl.14.37\%
\]

**EXAMPLE 5**

4-Ethyl-4'-fluoro-2-hydroxybenzophenone

3-Ethylphenol (24.4 g) and 4-fluorobenzoyl chloride (34.9 g) were reacted together as in Example 2 giving three main fractions: B (11.4 g) 126-129°C @ 0.07 mmHg; C (7.9 g), 129-132°C @ 0.06 mmHg; D (5.9 g), 132-150°C @ 0.06 mmHg, all containing ~ 80% of the required isomer. B (4.0 g) was separated by preparative thin layer chromatography to give the title compound (2.6 g), m.p. 44-48°C. The same compound was obtained using the method of Example 4.
EXAMPLE 6

4-Ethyl-4'-fluoro-2-hydroxybenzophenone oxime.

4-Ethyl-4'-fluoro-2-hydroxybenzophenone (21.0 g, 80% pure) was treated with hydroxylamine hydrochloride (24.0 g) in a manner similar to that in Example 3, to give, after recrystallisation from benzene, the title compound as a white crystalline solid (10.7 g), m.p. 130-2°C. Microanalysis: C_{15}H_{14}FNO requires 69.5%C, 5.4%H, 5.4%N, 7.3%F; found 69.2%C, 5.5%H, 5.2%N, 7.2%F.

EXAMPLE 7

2-Hydroxy-3-methyl-4'-chlorobenzophenone oxime

The ketone of Example 4 (7.5 g, 0.03 mole) in ethanol (18 ml.) was added with stirring to a solution of (85%) potassium hydroxide (20.74 g, 0.3 mole) in water (85 ml) at 10°C, this colloidal solution was treated with solid hydroxylamine hydrochloride (8.54 g, 0.12 mole) and stirred overnight. The solution was acidified with 5N HCl to give a solid, which was filtered, washed with water and stirred for 45 minutes, then treated with 5% Na_{2}CO_{3} solution (30.5 ml), to remove unwanted oxime stereoisomer, filtered, washed with 5% Na_{2}CO_{3} solution (100 ml) and then with water until free of alkali. The dried solid had m.p. 175-177°C. Recrystallisation from 54% benzene-light petroleum (b.p. 60-80°C) mixture gave the oxime, m.p. 178°C ("strained isomer") 5.45 g.

found: C.64.25; H.4.79; Cl.13.41; N.5.3%

C_{14}H_{12}ClCO_2 requires:  C.64.25; H.4.6; Cl.13.55; N.5.35%

EXAMPLE 8

2-Hydroxy-3-methyl-4'-chlorobenzophenone oxime acetate.

Acetic anhydride (12 ml) was warmed to 60°C. and treated with the oxime...
of Example 7 (5.25 g, 0.02 mole). The stirred mixture was warmed to 80°C to dissolve the oxime and the solution was then immediately cooled in an ice bath. The precipitated solid was filtered off, washed with light petroleum (b.p. 40-60°C) to give the acetate, 4.8 g, m.p. 154-156°C.

found: C 63.18; H 4.86; Cl 11.5; N 4.77
requires: C 63.26; H 4.64; Cl 11.67; N 4.67

EXAMPLE 9

2-Hydroxy-3-ethylbenzophenone

This compound (44.67 g) was prepared from benzene (172 g, 2.2 mole) and 2-hydroxy-3-ethyl benzoic acid chloride (63.15 g, 0.34 mole), using the same conditions as in Example 4. The b.p. of the compound was 123-126°C, / 0.14 mm, η²² 1.6081, ν max. (film) 1630 cm⁻¹. The same compound was obtained using the method of Example 2.

EXAMPLE 10

2',4'-Dichloro-3-ethyl-2-hydroxybenzophenone

Aluminium chloride (26.7 g) was added in portions to a stirred mixture of 2-ethylphenol (12.2 g) and 2,4-dichlorobenzoyl chloride (23.1 g) in 1,1,2,2-tetrachloroethane (100 ml), and then the mixture was heated under reflux for 21 hours. On cooling, the solution was poured onto concentrated hydrochloric acid (100 ml) cooled with ice (200 g). The organic fraction was separated and combined with two further chloroform washings of the aqueous fraction, and then this was twice washed with 10% aqueous sodium carbonate solution, dried over magnesium sulphate monohydrate and evaporated to a dark viscous oil (30.0 g). This oil was distilled in vacuo, the first fraction (156-172°C at 0.06 mmHg) containing 85% of the required product. (With ferric chloride solution a purple colour was obtained indicating the
presence of an o-hydroxyketone). The ketone product was purified by chromatography on a silica column $\eta_D^{22} 1.6163$. The same product was obtained using the method of Example 4.

EXAMPLE 11

4-Ethyl-3'-fluoro-2-hydroxybenzophenone

This compound was prepared from 3-ethylphenol (12.2 g), 3-fluorobenzoyl chloride (17.5 g) and aluminium chloride (26.7 g) in 1,1,2,2-tetrachloroethane (75 ml) using the same conditions as in Example 2, but heating under reflux, not at 105°C. The product was purified by chromatography on a silica column m.p. between 0 and 20°C. $\eta_D^{22} 1.5962$. The same product was obtained using the method of Example 4.

EXAMPLE 12

4-Chlorobenzoylchloride (1.35 g, 0.0077 mole) was added dropwise to a solution of 4-ethylphenol (0.86 g, 0.0070 mole) in 2.5 N aqueous sodium hydroxide (5.6 ml). The mixture was shaken vigorously for 15 minutes when a light brown solid separated out. The mixture was diluted with water (10 ml) and the solid was filtered off, washed with water (3 x 20 ml), and dried. The solid was recrystallised twice from n-hexane to yield pale brown crystals of 4-ethylphenyl-4-chlorobenzoate, m.p. 66.5-67°C.

The above ester (2.6 g) was heated with aluminium chloride (1.33 g) in tetrachloroethane for 6 hours at 125°C. A sample taken at the end of this time was added to dilute hydrochloric acid and the organic material was extracted into chloroform. Vapour phase chromatographic analysis of this solution detected no remaining ester, and comparison with an authentic sample showed the product to be 4'-chloro-5-ethyl-2-hydroxybenzophenone.
Similarly prepared were:
5-Ethyl-2-hydroxy-4'-methylbenzophenone, m.p. 49-51°C and
4'-Chloro-3,5-diethyl-2-hydroxybenzophenone b.p. 188°C at 1.4 mm/Hg.

**EXAMPLE 13**

2-Benzoyloxy-5-ethyl-4'-chlorobenzophenone

2-Hydroxy-5-ethyl-4'-chlorobenzophenone (5 g, 0.019 mole) was stirred vigorously in a solution of NaOH (7.5 g, 0.187 mole) in water (75 ml) and benzoyl chloride was added dropwise over 5 minutes. The temperature rose to around 50°C. The mixture was stirred for 1.5 hours at room temperature and was then extracted with ether, the ether washed with saturated NaCl solution, dried (Na₂SO₄), filtered and evaporated to leave the product, which was recrystallised from n-hexane to give white crystals of the desired product, m.p. 79-81°C.

**EXAMPLE 14**

2-Acetoxy-4'-chloro-5-ethylbenzophenone

2-Hydroxy-5-ethyl-4'-chlorobenzophenone (3 g), in acetic anhydride (10 ml) and acetic acid (1 ml) were refluxed for 3.5 hours, and allowed to cool. The mixture was poured into dilute NaOH solution and extracted with chloroform. The chloroform was washed with 10% NaHCO₃ solution (50 ml), dried (MgSO₄) and evaporated to leave an oil which was distilled, b.p. 160-165°C at 3.5 mm/Hg (2.3 g) to give the desired product.
EXAMPLE 15

5-Ethyl-2-hydroxy-4'-trifluoromethyl benzophenone

Aluminium chloride (0.6 g, 0.004 mole) was stirred in dichloromethane (2 ml) and treated with 4-trifluoromethylbenzoyl chloride (1 g, 0.0048 mole) (ice-bath cooling) and then with 4-ethylanisole (0.6 g, 0.0044 mole) in dichloromethane (1 ml). The mixture was stirred at room temperature overnight and then poured into ice and concentrated hydrochloric acid and extracted with chloroform. The chloroform solution was washed with 10% NaHCO₃ solution (100 ml), dried (MgSO₄), filtered and evaporated to leave 5-ethyl-2-methoxy-4'-trifluoromethylbenzophenone (1.2 g) as a yellow oil. The latter was heated in 55% aqueous hydrogen bromide (27.5 ml) at 110-120°C, for 5 hours. The mixture was evaporated to dryness to leave the required product.

EXAMPLE 16

5-Ethyl-2-hydroxy-3'-carboxy- and 3'-carbomethoxybenzophenone

Aluminium chloride (39.9 g, 0.3 mole) was stirred in dichloromethane (133 ml) and treated with 3-carbomethoxybenzoyl chloride (59.5 g, 0.3 mole) (ice-bath cooling), over 0.5 hours. 4-Ethylanisole (40.8 g, 0.3 mole) in dichloromethane (70 ml) was added to the stirred, cooled mixture, which was then stirred at room temperature overnight. The reaction mixture was processed as in Example 15 to leave 5-ethyl-2-methoxy-3'-carbomethoxybenzophenone. The latter was heated in 55% aqueous hydrogen bromide (500 ml) at 110-120°C for 5 hours. The mixture was evaporated to dryness to leave 5-ethyl-2-hydroxy-3'-carboxybenzophenone, which was characterised by having the correct C, H and N microanalysis. The latter carboxylic acid was then refluxed overnight in methanol (500 ml) containing concentrated sulphuric acid (5 ml), poured into water (1 L) and extracted with ether. The combined ethereal extracts were washed with saturated NaHCO₃ solution, dried (MgSO₄), filtered and evaporated to leave the desired ester, which gave a satisfactory microanalysis.
The claims defining the invention are as follows.

1. A pharmaceutical formulation containing an active ingredient in association with a pharmaceutically acceptable carrier therefor, said active ingredient being a compound of the formula:

\[
\begin{align*}
\text{Ar} & \quad \text{R}^1 \quad \text{C} \quad \text{Z} \\
\text{R}^2 & \quad \text{R}^3 \\
\end{align*}
\]

wherein \( R^2 \) is hydrogen or ethyl, \( R^1 \) and \( R^3 \) represent hydrogen, methyl or ethyl, at least one of \( R^1 \), \( R^2 \) and \( R^3 \) not being hydrogen; \( \text{Ar} \) is a phenyl group optionally substituted by from one to three groups selected from chlorine, fluorine, methyl, carboxy, \( \text{COOR}^5 \) and trifluoromethyl; \( Z \) is hydrogen or \( \text{COR}^5 \); and \( Y \) is \( \text{O}, \text{NO}_2 \) or \( \text{NOCOR}^5 \), \( R^5 \) being \( C_{1-4} \) alkyl or phenyl, provided that

(i) when \( \text{Ar} \) is 4-chlorophenyl, \( Y \) and \( Z \) are as defined above and \( R^1 \) and \( R^2 \) are hydrogen, \( R^3 \) is methyl;

(ii) when \( \text{Ar} \) is unsubstituted phenyl, \( Z \) is as defined above, \( R^1 \) and \( R^2 \) are hydrogen and \( R^3 \) is ethyl, \( Y \) is \( \text{O} \);

(iii) when \( R^1 \) is ethyl, \( R^2 \) and \( R^3 \) are hydrogen and \( Y \) and \( Z \) are as defined above, \( \text{Ar} \) is not 2,4- or 3,4-dichlorophenyl, 2- or 3-chlorophenyl or 4-fluorophenyl;

2. A formulation as claimed in claim 1, wherein \( R^1 \), \( R^2 \) and \( R^3 \) are as defined in claim 1, \( \text{Ar} \) is a phenyl group optionally substituted by from one
to three groups selected from chlorine, fluorine or methyl, Z is hydrogen or COR, and Y is 0, NOH or NCCOR, R being as defined in claim 12.

3. A formulation as claimed in claim 1, wherein one of R¹, R² and R³ is ethyl and the others are hydrogen; Ar is phenyl, 4-chlorophenyl, 4-fluorophenyl or 4-methylphenyl; Z is hydrogen; and Y is 0.

4. A formulation as claimed in claim 1, wherein Z is hydrogen; Y is 0 and either

(i) R¹ is ethyl; R² and R³ are hydrogen and Ar is 4-chlorophenyl;
(ii) R³ is ethyl; R¹ and R² are hydrogen and Ar is 2,4-dichlorophenyl; or
(iii) R² is ethyl; R¹ and R³ are hydrogen and Ar is 3- or 4-fluorophenyl.

5. A formulation as claimed in any one of claims 1 to 4, in a dosage unit form containing from 5 to 500 mg. of said active ingredient.

Dated this 10th day of May, 1979
LILLY INDUSTRIES LIMITED
by its Patent Attorneys
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