2,3-BIS(p-METHOXYPHENYL)-INDOLE-5-CARBOXYLIC ACID DERIVATIVES

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3 Claims

ABSTRACT OF THE DISCLOSURE

Intermediates having the formula:

wherein R is H, C₂H₅ or —CH₂—CH₂OH are used to produce anti-inflammatory indoles of the formula:

CROSS-REFERENCES TO RELATED APPLICATIONS

This application is a division of application Ser. No. 794,402 filed Jan. 27, 1969, now U.S. Patent No. 3,565,912.

BACKGROUND OF THE INVENTION

Field of the invention

The present invention is concerned with new organic compounds and more particularly with novel 5-lower-alkanoyl-2,3-bis(p-methoxyphenyl)indoles (IX), intermediates for the production thereof and the process therefor.

SUMMARY OF THE INVENTION

The novel compounds and the process of this invention can be illustratively represented by the following sequences of formulae:
3,654,308

Method B

wherein \( R_1 \) is a lower alkyl of 1 to 4 carbon atoms, inclusive; \( R_2 \) is selected from the group consisting of hydrogen and lower alkyl of 1 to 3 carbon atoms, inclusive; \( R_3 \) is selected from the group consisting of lower alkyl and lower alkanol of 1 to 4 carbon atoms, inclusive, and \( R_4 \) is selected from the group consisting of \(-\text{CH}_2\text{CH}_2\text{OH} \) and \( R \).

The desired end product can therefore illustratively be shown by the Formula IX

\[
\text{IX} \quad \text{IV} \quad \text{XII} \quad \text{VIII}
\]

wherein \( R_0 \) is selected from the group consisting hydrogen and lower alkyl of 1 to 3 carbon atoms, inclusive, and \( R' \) is selected from the group consisting of hydrogen, and alkyl and alkanol of 1 to 4 carbon atoms, inclusive.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Examples of lower-alkyl of 1 to 3 carbon atoms, inclusive, are methyl, ethyl, propyl and isopropyl; examples of alkyl of 4 carbon atoms, inclusive, are butyl isobutyl and tert. butyl.

Examples of lower-alkanol of 1 to 4 carbon atoms are formyl, acetyl, propionyl, butyryl and isobutyryl.

The process of Method A of this invention comprises the following steps: Heating an alkalylester of \( p \)-aminobenzoic acid (I) with anisole in the presence of an acid catalyst e.g., \( p \)-toluenesulfonic acid, to give at first the intermediate alkyl \( \text{p-[(p-methoxy-}\text{-a-(p-methoxyphenyl)}\text{-phenacylamino]}\text{benzoate, which by further heating with} \) p-aminobenzoate and an acid catalyst gives alkyl \( 2,3\)-bis\( (p\text{-methoxyphenyl})\text{indole-5-carboxylate II; saponifying II with} \) an alkali hydroxide and treating the resulting salt with an acid to obtain the free \( 2,3\)-bis\( (p\text{-methoxyphenyl})\)indole-5-carboxylic acid (III); converting III with thionyl chloride to the acyl chloride and treating the acyl chloride in the presence of cadmium chloride with an alkyl magnesium halide, \( R_0\text{MgX} \) in which \( R_0 \) has from 1 to 3 carbon atoms, inclusive, to obtain the compound of Formula IV in which \( R_0 \) is alkyl of 1 to 3 carbon atoms, inclusive.

If a compound of Formula IV in which \( R_0 \) is hydrogen is wanted, the acyl chloride is reduced with hydrogen in the presence of a palladium catalyst supported on barium sulfate. [Rosenmund Reduction, Ber. 51, 585 (1918)].

The compounds of Formula V are made by treating the compounds of Formula IV with sodium hydrate and an alkyl halide (for \( R_3 \) is alkyl) or acyl halide (for \( R_3 \) is alkanol) (see J. Szmuszkovicz, J. Med. Chem. 9, 527 (1966)).

The process of Method B of this invention comprises the following steps: Heating a carbalkoxyphenylhydroazine VI with deoxyxyaninol and refluxing the resulting reaction mixture containing VII with ethanol +HCl or ethylene glycol to give the corresponding ester of \( 2,3\)-bis\( (p\text{-methoxyphenyl})\)indole-5-carboxylic acid (VIII). Treating compound VIII like compound II with an alkaline hydroxide and then with an acid produces \( 2,3\)-bis\( (p\text{-methoxyphenyl})\)indole-5-carboxylic acid III, which can be converted to compounds of Formula IV and V as shown above.

The compounds of Formula IX of the present invention are anti-inflammatory, analgesic and antipyretic agents useful in birds and mammals. The compounds are useful topically, orally and parenterally for the relief of rheumatic, allergic, dermatological and ocular conditions generally responsive to anti-inflammatory agents, and for the relief of pain and fever.

More specifically, the compositions of the present invention are useful for the reduction of swelling in gouty arthritis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, psoriatic arthritis, acute superficial thrombo- phlebitis and painful shoulder syndromes such as peri- tendinitis, capsulitis, bursitis, and acute shoulder arthritis as well as contact dermatitis, atopic dermatitis, neurodermatitis, anogenital pruritus, seborrhoeic dermatitis, and the like, and for the relief of pain and fever.

The novel compositions also find application in the local treatment of inflammatory conditions in animal mastitis, a disease of the mammary glands which can be of particular concern in milk-producing animals such as cows.

The compounds of the present invention in the treatment of inflammatory conditions compare more favorably with phenylbutazone, an accepted non-steroid employed in the treatment of gout, rheumatoid arthritis, ankylosing spondylitis and other inflammatory conditions. Thus, e.g., in the hind paw edema assay utilizing both intact and adrenalectomized rats, 5-acetyl-2,3-bis\( (p\text{-methoxyphenyl})\)indole in a 1% aqueous sodium carboxymethylcellulose vehicle is about 3 to 4 times as active as phenylbutazone.
In the hind paw edema assay, male rats, intact or adrenalectomized, weighing about 160–200 grams are fasted for about 14 hours. The animals are dosed orally with 1.0 ml of a suspension (4.5% w/v) in glycerol. The edema is measured by proudness of a 1% aqueous sodium carboxymethylcellulose solution, or with 1.0 ml of a solution in dimethyl sulfoxide, one hour prior to injection of 0.1 ml of 0.5% aqueous carrageenin into the right hind paw. The left hind paw serves as a control. Five hours after carrageenin injection both paws are amputated and weighed. The ability of compounds to inhibit carrageenin-induced edema is considered to be of value in determining efficacy of potential anti-inflammatory therapeutic agents.

The pharmaceutical forms contemplated by this invention include pharmaceutical compositions suited for topical, oral, parenteral and rectal use. The term "unit dosage form" as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier or vehicle. The specifications for the novel unit dosage forms are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved and (b) the limitations inherent in the art of compounding such an active material for therapeutic use, as disclosed in detail in this specification, these being features of the present invention. Examples of suitable unit dosage forms, as herein described, are tablets, capsules, pills, powder packets, wafers, cachets, granules, solutions or suspensions for oral or sterile injectable use, suppositories, and segregated multiples of any of the foregoing, and other forms sulfided to herein.

The term "topical" as employed herein relates to the use of the medicament, incorporated in a suitable base or vehicle, at the site of the inflammation for exertion of local action. Accordingly, such topical compositions include those pharmaceutical forms in which the medication is applied externally by direct contact with the surface to be treated. Conventional pharmaceutical forms for this purpose include ointments, lotions, pastes, jellies, sprays, powders, and the like. The term "ointment" embraces formulations (including creams) having oleaginous absorption, water-soluble and emulsion-type bases, e.g., petrolatum, lanolin, polyethylene glycols, as well as mixtures of these compositions. In the present invention also include those pharmaceutical forms which afford local as opposed to systemic release into the immediately affected areas where such areas are not accessible for direct external application, such forms being sprays (e.g., for oral or nasal use), aerosols (e.g., for deeper penetration than is usually afforded by a spray), drops (e.g., for use in the eyes and ears), suppositories (e.g., for rectal or vaginal use), and powders (e.g., for insufflation.)

The oral dosage forms include both solid and liquid. Solid unit dosage forms can be in the form of tablets, coated or uncoated; capsules, hard or soft; powders; granules; pills, and the like. Suitable vehicles or carriers for such compositions include lipids, carbohydrates, proteins and mineral solids. The tablets for oral use contain the active ingredient in the required amount with pharmaceutical diluents or excipients, binders, disintegrators, and lubricants. The active ingredient, suitably compounded with a carbohydrate diluent (e.g., lactose), a mineral solid (e.g., calcium sulfate and dicalcium phosphate), and the like, to form the basic powder mixture. The said mixture can be granulated by wetting with a protein binder such as gelatin solution, or a carbohydrate such as azevita mucilage and corn syrup, and is then screened to desired particle sizes. As an alternative to granulating, the mixtures can be "slugged" and the slugs broken down into suitable size granules prior to compression of the final tablets. A carbohydrate disintegrating agent (e.g., corn starch) is advantageously added at the time of preparing the basic mixture. The lubricant, for example, a lipid (such as stearic acid, a stearate salt or mineral oil), a mineral solid (such as colloid mill), and the like, is used to prevent sticking of the mixture to the tablet-forming dies. The tablets can be coated or left uncoated. Suitable coatings include a sealing coat of shellac, a taste-disguising coating (such as sugar or methylcellulose), and a lipid coating such as carnauba wax. Special coatings can comprise (a) lipid-type compounds (e.g., lecithin), and the like, is used to prevent sticking of the active ingredient to provide sustained action, or (b) enteric substances (such as styrene-maleic acid copolymer and cellulose acetate phthalate) to resist release of the active ingredient in the stomach and permit release in the upper intestine.

The capsules for oral use can comprise a mixture of the active ingredient in combination with a pharmaceutical diluent and a gelatin sheath enclosing said mixture. The capsules can be in the form of soft capsules enclosing the active ingredient in the required amount, e.g., soft elastic capsules can be filled with the drug in solution or suspension in oil, oil-organic solvent, polyborate 80 or polystyrene-80 oil mixture. Hard capsules can also be prepared comprising mineral solids (e.g., talc or calcium sulfate) and, optionally, lubricants (e.g., calcium or magnesium stearate) with the required amount of the drug.

The powders for oral use are conveniently prepared by comminuting the active ingredient and mixing with an acceptable diluent (e.g., an edible carbohydrate such as lactose) and advantageously include sweetening and flavoring agents (such as sugar, saccharin, a cyclamate salt or flavoring oil).

Pills for oral use include the required amount of the active ingredient plus suitable binders, binders, disintegrators and lubricants as heretofore set forth with respect to tablets and capsules. The pills are suitably prepared by the rolling technique or other known methods, advantageously with the use of the aforesaid lubricants.

For the treatment of domestic birds and mammals by oral administration, the therapeutic ingredient is conveniently prepared in the form of a food premix. The food premix can comprise the active ingredient in admixture with an edible diluent such as starch, oatmeal, flour, calcium carbonate, talc, dried fish meal and like nontoxic, orally-acceptable diluents. The prepared premix is then conveniently added to the regular feed, thereby supplying the included medication to the animal or bird in the course of feeding.

The liquid compositions for oral use can be in the form of suspensions, emulsions, or solutions, in aqueous and non-aqueous vehicles such as edible vegetable oils.

The emulsions are preferably of the oil-in-water type and contain the active ingredient in the required amount with acceptable emulsifying agents, such as gum acacia, gum tragacanth, naturally-occuring phosphatides, and the like. Suitable sweetening, coloring, and flavoring agents are added to the aforesaid phase of the emulsion. Under ordinary conditions of storage and use, the emulsions are kept free from microorganism growth by the addition of a preservative, such as methylparaben and propylparaben. Solutions for oral use of the active ingredient can be prepared in an edible vegetable oil such as in corn oil, cottonseed oil, peanut oil, coconut oil, sesame oil, safflower oil, and the like. To increase the amount of active material dissolved in the oil, the drug can be dissolved first in about 5 to 25% of an oral, pharmaceutically acceptable organic solvent such as N,N-dimethylacetamide, dimethyl sulfoxide or 2,2-dimethyl-4-carbinol-1,3-dioxolane. Antioxidants can be added. Alternatively, the emulsions can be prepared in any of the above organic solvents or mixtures of these. Sweetening, coloring and flavoring agents are added to assure patient acceptance.

Suspensions for oral use are conveniently prepared in water and aqueous solutions of orally acceptable liquids,
such as ethanol, glycerol, sorbitol, propylene glycol and polyethylene glycols. The active ingredient is normally comminuted to a fine particle size for use in the suspensions, which can also contain soluble suspending agents, such as sodium carboxymethylcellulose, methylcellulose, acacia, tragacanth, polyvinylpyrrolidone, polyvinyl alco-
hol, and the like. As with the other liquid oral compositions, preservatives, coloring agents, sucrose and other sweeteners, and flavoring agents are added for convenience in storage and use.

It has been noted that good blood levels of oral preparations can be obtained by utilizing the active drug in a fine particle size of about 10 microns or less and more preferably, less than 1 micron. Illustratively, a 5-acetyl-
2,3-bis(p-methoxyphenyl)indole having fine particle size can be prepared by slowly adding, with good agitation, an absolute ethanol solution of a pure Formula IX compound to cold water (e.g., about 1 to 5°C), and separating the resulting fine precipitate.

Moreover, blood levels are also greatly increased, when the active compound is given orally as a dispersion in one of the above non-aqueous vehicles, particularly when given in an edible vegetable oil such as cottonseed oil, corn oil, safflower oil, sesame oil, peanut oil, olive oil, coconut oil, and the like. A higher concentration of the active compound in solution in vegetable oil can be obtained by first dissolving the active compound in a non-toxic, pharmaceutically acceptable organic solvent, e.g., N,N-dimethylacetamide, dimethyl sulfoxide or 2,2-dimethyl-1,3-dioxolane, and then diluting the solution with the oil. The final vehicle may contain up to about 50% v/v. or more of the organic solvent, depending on the concentration of active compound desired, and preferably about 5 to 25% of organic solvent.

Improved blood levels of the active compound can also be obtained by adding a surfactant such as Aerosol OT or Aerosol OTB, polysorbate 80, sodium laurel sulfate, Pluronic F68, and the like, to oral preparations. Aerosol OTB is particularly suitable for use with the finely powdered drug in tablets or hard gelatin capsules and polysorbate 80 is particularly useful with solutions of the drug in oil, organic solvent, or oil-organic solvent. Improved blood levels can also be obtained by utilizing the surfactant alone with the active compound. Thus, e.g., a solution of 5-acetyl-
2,3-bis(p-methoxyphenyl)indole in polysorbate 80 in a soft elastic capsule results in unexpectedly superior blood levels.

The parenteral dosage forms of the present invention for intramuscular, subcutaneous, intra-articular and intrabursal use include sterile solutions and suspensions, and sterile powders for the extemporaneous preparation of sterile injectables. In the case of sterile suspensions and powders, it is preferred that the active ingredient be of fine particle size, as alluded to above in connection with oral preparations. The solvent or suspending liquid comprises water, vegetable oils, or organic solvents, e.g., glycerol, propylene glycol, liquid polyethylene glycol, di-
methyl sulfoxide, N,N-dimethylacetamide, 2,2-dimethyl-
4-carbonil-1,3-dioxolane, isopropyl myristate, polysorbate 80, ethanol, benzyl alcohol, benzyl benzoate, and the like, or suitable mixtures thereof.

In the preparation of sterile powders for use in sterile injectables, the preferred method involves freeze-drying of a previously sterilized solution of the active ingredient plus any additional desired soluble ingredients to obtain a sterile, dry product. Powders for Injectable suspensions are preferably sterilized by the use of a gas, such as ethyl-
ene oxide, after blending with the required additional ingredients in the proper particle size. Just prior to use, the sterile powder is reconstituted in the desired sterile suspending liquid.

The dosage of a 5-alkanoyl-2,3-bis(p-methoxyphenyl) indole of Formula IX dispersed in a pharmaceutically and physiologically acceptable carrier ranges from about 10 to about 1000 mg. in a single dose or in divided doses given one to four times daily and preferably, 50 mg. to 1500 mg. one to four times a day, depending on the age, weight, and condition of the patient, and frequency and route of administration.

The preferred oral dosage is 100–1000 mg. three or four times a day. Preferably liquid oral preparations contain about 0.5 to about 5% w/v. of the active ingredient.

For topical use the preferred concentration is 0.5 to 10% and more preferably 1 to 5% and preferably in a dissolved state.

Various other active ingredients can be included in the formulations of the present invention to provide a supplementary effect which when employed in the treatment of certain conditions enhances the usefulness of the 5-alkanoyl-2,3-bis(p-methoxyphenyl)indoles of Formula IX. Advantageous combinations of activity and syner-
ergistic action can be obtained. Thus, the 2,3-bis(p-meth-
ophenoxynyl)indoles can be effectively combined with other anti-inflammatory agents such as phenylbutazone (50–100 mg.), oxypenbutazone (50–100 mg.), 6x-methyl-
 prednisolone (0.5–10 mg.), hydrocortisone (5–25 mg.), fluroroprednisolone (0.5–5 mg.), and prednisone or prednisolone (0.5–15 mg.); analgesic agents such as aspirin (150–600 mg.), N-aceptyl-p-aminophenol (150–600 mg.), salicylamide (150–600 mg.), acetylsalicylin (150–600 mg.), codeine (10–60 mg.); muscle relaxants such as carisoprodol (200–250 mg.), chlorphenesin carbamate (200–500 mg.), chloroxzone (250–500 mg.), methocarbamol (250–500 mg.); tranquilizers such as meprobamate (200–400 mg.), ecticurea (150–600 mg.), chlordiazepoxide (5–50 mg.), phenoglycol (200–400 mg.); antidepressants such as methylphenidate (5–20 mg.); imipramine (10–100 mg.); amitriptyline (10–100 mg.); tranlyclpromine (10–50 mg.); sedatives such as butobarbital or phenobarbital (8–60 mg.), amobarbital (15–120 mg.), methypyrrol (50–100 mg.); antispasmodics such as methscopolamine bromide (1.5–5 mg.), halomiprine methylbromide (0.5–5 mg.), propantheline bromide (2–5 mg.); vitamins such as ascorbic acid (as sodium ascorbate), B-complex; antibiotics such as chloramphenicol, lincomycin, penicillin, tetracyclines, novobiocin, erythromycin, neomycin, polymyxin, baci-
larin, nystatin.

FORMULATIONS

(1) Tablets

One thousand tablets for oral use, each containing 200 mg. of 5-acetyl-2,3-bis(p-methoxyphenyl)indole, are prepared from the following ingredients:

Gm.  
1. acetyl - 2.3 - bis (p-methoxyphenyl)indole (very finely divided) .................. 200  
Dicalcium phosphate, N.F. .................................................. 200  
Methylcellulose, U.S.P. (15 cps.) ..................................... 6.5  
Talc .......................................................... 30  
Calcium stearate ..................................................... 3.5

The 5-acetyl-2,3-bis(p-methoxyphenyl)indole and dicalcium phosphate are mixed well, granulated with 7.5% w/v. solution of methylcellulose in water, passed through a No. 8 screen and dried carefully. The dried granules are passed through a No. 12 screen, mixed with the talc and stearate and compressed into tablets.

Following the above procedure, tablets are similarly prepared substituting 25, 50, 250 and 500 gm. of 5-
acetyl-2,3-bis(p-methoxyphenyl)indole for the 200 gm. of the example to prepare tablets having 25, 50, 250 and 500 mg. amounts, respectively, of the compound.

To improve the blood levels of the principal active ingredient, about 1% by weight of the latter of diocetyl sodium sulfosuccinate is added to the tablet. This is incor-
porated as a fine powder in the initial mixture before granulating or by dissolving in the granulating solution.
The preceding tablets can be administered to dogs and cats at a daily dose of from 0.4 to 100 mg./kg. body weight for the treatment of rheumatoid arthritis.

(2) Hard gelatin capsules

One thousand two-piece hard gelatin capsules for oral use, each capsule containing 150 mg. of 5-acetyl-2,3-bis(p-methoxyphenyl)indole, are prepared from the following ingredients:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Gm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-acetyl-2,3-bis(p-methoxyphenyl)indole</td>
<td>150</td>
</tr>
<tr>
<td>Corn starch</td>
<td>150</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>25</td>
</tr>
</tbody>
</table>

The finely powdered ingredients are mixed thoroughly, then filled into hard gelatin capsules of appropriate size. For improved blood levels, 1.5 gm. of finely powdered dioctyl sodium sulfosuccinate is mixed thoroughly with the rest of the ingredients before encapsulating.

(3) Hard gelatin capsules

One thousand two-piece hard gelatin capsules for oral use, each containing 100 mg. of 5-acetyl-2,3-bis(p-methoxyphenyl)indole and 1 mg. of 6a-methylprednisolone, are prepared from the following ingredients:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Gm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-acetyl-2,3-bis(p-methoxyphenyl)indole (fine particle size)</td>
<td>100</td>
</tr>
<tr>
<td>6a-methylprednisolone</td>
<td>1</td>
</tr>
<tr>
<td>Corn starch</td>
<td>150</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>15</td>
</tr>
</tbody>
</table>

One or two capsules three times a day will relieve pain and inflammation in acute gouty arthritis.

(4) Aqueous oral suspension

An aqueous oral suspension containing in each five milliliters 150 mg. of 5-acetyl-2,3-bis(p-methoxyphenyl)indole is prepared from the following ingredients:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Gm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-acetyl-2,3-bis(p-methoxyphenyl)indole (fine particle size)</td>
<td>300</td>
</tr>
<tr>
<td>Methylparaben, U.S.P.</td>
<td>7.5</td>
</tr>
<tr>
<td>Propylparaben, U.S.P.</td>
<td>2.5</td>
</tr>
<tr>
<td>Saccharin sodium</td>
<td>12.5</td>
</tr>
<tr>
<td>Cyclamate sodium</td>
<td>2.5</td>
</tr>
<tr>
<td>Glycerin</td>
<td>3000</td>
</tr>
<tr>
<td>Tragacanth powder</td>
<td>100</td>
</tr>
<tr>
<td>Orange oil flavor</td>
<td>10</td>
</tr>
<tr>
<td>F.D. and C. orange dye</td>
<td>7.5</td>
</tr>
<tr>
<td>Deionized water</td>
<td>10,000</td>
</tr>
</tbody>
</table>

(5) Topical ointment

One thousand grams of a topical ointment containing 5% of 5-acetyl-2,3-bis(p-methoxyphenyl)indole and 0.6% neomycin sulfate is prepared from the following ingredients:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Gm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-acetyl-2,3-bis(p-methoxyphenyl)indole (fine particle size)</td>
<td>50</td>
</tr>
<tr>
<td>Neomycin sulfate (micronized)</td>
<td>6</td>
</tr>
<tr>
<td>Light liquid petrolatum</td>
<td>250</td>
</tr>
<tr>
<td>Wool fat</td>
<td>200</td>
</tr>
<tr>
<td>White petrolatum, q.s.</td>
<td>1000</td>
</tr>
</tbody>
</table>

The ointment is usefully applied to the skin for the local treatment of infection and inflammation.

(6) Soft elastic capsules

One thousand soft elastic capsules for oral use, each containing 50 mg. of 5-acetyl-2,3-bis(p-methoxyphenyl)indole, are prepared from the following ingredients:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Gm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-acetyl-2,3-bis(p-methoxyphenyl)indole (fine powder)</td>
<td>50</td>
</tr>
<tr>
<td>N,N-dimethylacetamide (DMA)</td>
<td>25</td>
</tr>
<tr>
<td>Corn oil, U.S.P., q.s.</td>
<td>500</td>
</tr>
</tbody>
</table>

The 5-acetyl-2,3-bis(p-methoxyphenyl)indole is first dissolved in the DMA. Then the oil is added with stirring until a clear solution is obtained. Each capsule is filled with 0.5 ml. of the solution. One or two capsules are used four times a day to relieve pain, fever, and inflammation in rheumatoid arthritis.

The above solution, instead of being filled into capsules, can be used as a nasal solution and administered in a teaspoonful (5 ml) dose twice a day for the same purpose as the soft elastic capsules above.

The above solution, instead of being filled into capsules, can be used for intramuscular injection after suitable sterilization. One or two milliliters (100 or 200 mg. of active material) is used one to three times a day for the same purpose as the soft elastic capsules above.

(7) Oral fluid

One thousand milliliters of an oral fluid containing 150 mg. of 5-acetyl-2,3-bis(p-methoxyphenyl)indole in each 5 ml. is prepared from the following ingredients:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Gm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-acetyl-2,3-bis(p-methoxyphenyl)indole powder</td>
<td>30</td>
</tr>
<tr>
<td>Cottonseed oil, q.s.</td>
<td>1000</td>
</tr>
</tbody>
</table>

The oil is heated to 60° C. and the powder is added gradually with stirring until it is completely in solution. One or two teaspoonfuls (5 to 10 ml.) three times a day will relieve pain and inflammation in rheumatoid arthritis.

In carrying out the process of method A of this invention, anisoin and an alkyl p-aminobenzoate are condensed in about equimolar quantities in the presence of an acid catalyst. As acid catalyst, p-toluenesulfonic acid may be used. Generally, the alkyl p-amino benzoate is methyl or ethyl p-amino benzoate, but other p-amino benzoates such as propyl, isopropyl, butyl, isobutyl, pentyl and hexyl p-amino benzoates can be used.

The reaction is generally carried out in a solvent such as toluene, xylene, benzene, cyclohexane, methylecyclohexane and the like, at the reflux temperature of the reaction mixture. In the preferred embodiment, provisions are made to remove the water from the reaction mixture, generally by using a water trap. The product, which is thus obtained, is alkyl p-[(p-methoxy-a-(p-methoxyphenyl)phenacylamino)benzoate. The time of the reaction varies with the temperature and will be between 1 to 4 hours. The product is isolated from the reaction mixture by standard procedures e.g., evaporation of the solvent or extraction, and is purified by recrystallization.

The product is again treated with alkyl p-amino benzoate in the presence of an acid catalyst, such as drops of hydrochloric acid. In this second treatment of alkyl p-[(p-methoxy-a-(p-methoxyphenyl)phenacylamino)benzoate, no solvent is used and the temperature is increased to about 170-230° C. This temperature is provided by the use of an oil bath. The molar ratios of the two reagents in this second reaction is about 1:2 equivalents of alkyl p-[(p-methoxy-a-(p-methoxyphenyl)phenacylamino] benzoate to 1:1-2 equivalents of the alkyl p-amino benzoate. The time of reaction is between 2-12 hours and the reaction is performed in the preferred embodiment of this invention at 190-215° C. for a period of 3-6 hours while keeping the reaction mixture under an air condenser. After the reaction is terminated, the mixture is cooled and the product is generally isolated by chromatography or crystallization from acetone-Skellysolve B hexanes. In this manner, alkyl 2,3-bis(p-methoxyphenyl)indole-5-carboxylate (II) is obtained.

Compound II is saponified with sodium or potassium hydroxide in aqueous methanol or ethanol solution, usually by bringing the reaction mixture to reflux for a prolonged period of time. In the preferred embodiment of the invention, the sodium or potassium hydroxide is used in large excess, in about 5-10% concentration in a solvent consisting of 20-35% water with a balance of methanol or ethanol. The reaction time, at reflux temperature, is between 6-24 hours. At the termination of the reaction,
the mixture is evaporated, the product, a sodium or potassium salt, is extracted with water. The water solution is purified from undesirable organic products by extraction with ether and then acidified with an acid such as hydrochloric or sulfuric acid under cooling. The free acid, thus obtained, which is not soluble in water, can be purified by means of extraction, chromatography, recrystallization and the like. In this manner, pure 2,3-bis(p-methoxyphenyl) indole-5-carboxylic acid (III) is obtained.

The thus-obtained acid (III) is converted to the acid chloride by treatment with excess thionyl chloride in benzene solution at reflux temperature. Lower temperatures can also be used for this conversion such as temperatures between 60° to the reflux temperature of the mixture. At reflux temperature the reaction takes between 30 minutes to 2 hours, with longer periods required if the reaction is performed at a lower temperature. After the reaction is completed, the product is obtained by evaporating the mixture. The crude acid chloride thus-obtained, is used in the modified Grignard reaction without further purification.

The acid chloride is converted to an acyl compound by treatment with an alkyl Grignard in the presence of cadmium chloride. In the preferred embodiment of this invention, a solution of 5-15% of cadmium chloride in ether and an excess of an alkyl magnesium halide such as methyl, ethyl, propyl, isopropyl, and t-butylmagnesium halide or iodide in ether solution and 5-carboxyl-2,3-bis(p-methoxyphenyl)indole chloride is mixed together at room temperature. It is then heated to the reflux temperature for a period of 2-6 hours, cooled and decomposed with hydrochloric acid. The product is isolated by conventional procedures with organic solvents, for example, methylene chloride, chloroform, benzene or the like; and purified by chromatography, and/or recrystallization from organic solvents such as ethyl acetate, Skellysolve B hexanes, and the like. In this manner, 5-acetyl-2,3-bis(p-methoxyphenyl)indole is obtained.

If 5-formyl-2,3-bis(p-methoxyphenyl)indole is desired, 5-carboxyl-2,3-bis(p-methoxyphenyl)indole chloride is reduced with hydrogen in the presence of a palladium-on-barium sulfate or a nickel catalyst [Karl Rosenmund, Ber. 51, 585 (1918)].

To obtain N-acetyl or N-alkyl derivatives of the 5-acetyl-2,3-bis(p-methoxyphenyl)indole, the product is reacted first with a strong base, such as sodium hydride or potassium hydride to give the indole salt which is thereupon reacted with a selected alkyl halide or acid chloride to provide the 1-alkyl or 1-acyl derivatives of 5-acetyl-2,3-bis(p-methoxyphenyl)indole.

In carrying out the invention by process B, p-carbalkoxyphenylhydrizine and desoxyanisoin, in equal molar equivalents, are heated for a short period (5-15 minutes) to about 160-170° C. After cooling, an alcohol such as ethanol, methanol, ethylene glycol and the like is added in a large excess. If methanol or ethanol is used, hydrogen chloride must be added. The reaction mixture is heated for 12-36 hours. This provides the corresponding ester of 2,3-bis(p-methoxyphenyl)indole-5-carboxylic acid. After cooling, this desired ester (VIII) precipitates from the solution is recovered by filtration and purified by recrystallization from organic solvents. Treatment of the ester VIII with sodium or potassium hydroxide and thereupon with hydrochloric acid provides the free acid (III) which can be further transformed and converted to the products shown in Method A.

The following examples are illustrative of the process and products of the present invention, but are not to be construed as limiting.

EXAMPLE 1

Method A for ethyl-2,3-bis(p-methoxyphenyl)indole-5-carboxylate

(A) Ethyl p-[p-methoxy-a-(p-methoxyphenyl)phenacyl]amino)benzoate.—(A) A mixture of 27.2 g. (0.1 mole) of anisoin, 16.5 g. (0.1 mole) of ethyl p-amino-benzoate, a few crystals of p-toluene sulfonic acid, and 500 ml. of xylene was refluxed for 2 hours, using a water trap (1.5 ml. of aqueous solution such as hydrochloric or sulfuric acid under cooling). After cooling, the solution was washed with dilute hydrochloric acid, water, dilute aqueous sodium carbonate, and water and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a solid. Crystallization of the solid from acetone-Skellysolve B hexanes gave 30.6 g. (86% yield) of yellow prisms of melting point 37-38° C. A portion of the solid was recrystallized twice from acetone-Skellysolve B hexanes affording ivory prisms of ethyl p-{[p-methoxy-a-(p-methoxyphenyl)phenacyl]amino}benzoate of melting point 140.5-141.5° C.

U.V.: λ_max 222 (26,050); 299 (40,550).

(2) A mixture of 13.6 g. (0.05 mole) of anisoin, 8.26 g. (0.05 mole) of ethyl p-aminobenzoate, a few crystals of p-toluene sulfonic acid, and 500 ml. of benzene was refluxed for 22 hours using a water separator (0.6 ml. of aqueous layer collected). The benzene was evaporated giving an orange oil. A mixture of the oil and 250 g. of p-cymene was refluxed for 2 hours using a water separator (0.3 ml. of aqueous layer collected). The majority of this p-cymene was distilled at atmospheric pressure. A solution of the residue in ether was washed with dilute hydrochloric acid and water and dried with magnesium sulfate. The ether solution was concentrated and cooled giving a solid. Crystallization of the solid from acetone-Skellysolve B hexanes gave 13 g. of buff-colored prisms of ethyl p-[p-methoxyphenyl]phenacyl]amino)benzoate of melting point 139.5-141° C.

(B) 2,3-bis(p-methoxyphenyl)indole - 5-carboxylic acid.—A mixture of 0.1 g. of ethyl 2,3-bis(p-methoxyphenyl)indole-5-carboxylate, 5 ml. of water, 20 ml. of ethanol, and one pellet of potassium hydroxide was refluxed for 2 hours. The ethanol was evaporated. The residue was treated with ether and water. The aqueous layer was separated and acidified with dilute hydrochloric acid. The mixture was extracted with ether. The solution was dried over anhydrous magnesium sulfate, concentrated, and Skellysolve B was added. Cooling gave 49 mg. of small ivory needles of 2,3-bis(p-methoxyphenyl)indole-5-carboxylic acid of melting point 295-297° C.

EXAMPLE 2

Alternative method B for 2,3-bis(p-methoxyphenyl)-indole-5-carboxylic acid

(A) 2-hydroxyethyl ester of 2,3-bis(p-methoxyphenyl)indole-5-carboxylic acid.—A mixture of p-carbalkoxyphenylhydrizine (29.1 g.; 0.162 mole) (J. Gen. Chem. USSR, Engl. transl. 29, 3581 (1959); M.P. 112-114° C) and desoxyanisoin (41.5 g.; 0.162 mole) was stirred and heated at 160-170° C for 10 minutes. The mixture was cooled, 485 ml. of ethylene glycol was added and the mixture was refluxed for 21 hours. It was then cooled in ice until crystallization was complete, the solid was filtered and washed with ethylene glycol (2×50 ml.). Crystallization from ethanol afforded 31.7 g. (47% yield) of 2-hydroxyethyl ester of 2,3-bis(p-methoxyphenyl)indole-5-carboxylic acid of melting point 209-210° C, raised to 211-212° C on recrystallization.

U.V.: sh. 239 (16,500); λ_max 272 (53,000); sh. 338 (9,200).

(B) Ethyl ester of 2,3-bis(p-methoxyphenyl)indole-5-carboxylic acid from p-carbalkoxyphenylhydrizine.—A mixture of p-carbalkoxyphenylhydrizine (18.0 g.; 0.1 mole) and desoxyanisoin (25.6 g.; 0.1 mole) was stirred and heated at 160-170° C for 10 minutes. It was then cooled, 250 ml. of 3% ethanolic hydrogen chloride was added, the mixture was refluxed for 3 hours, and allowed to stand during the weekend. The resulting suspension was filtered (filtrate A), and the solid crystallized from methylene chloride, filtered and washed with water; 1.3 g. of 2,3,5,6-tetakis(p-methoxyphenyl)pyrano[3,2-f]
indole-4(8H)-one of melting point 271–272° C, was obtained. Filtrate A was evaporated, 300 ml. of water was added, and the product was extracted with methylene chloride (4× 100 ml). The organic extract was washed with 5% hydrochloric acid (2× 50 ml.), 5% sodium hydroxide solution (2× 50 ml.), saturated salt solution, dried over anhydrous sodium sulfate and evaporated. A mixture of the residue (20 g.) and 200 g. of silica gel was placed on a 2 kg. column of silica gel and chromatographed with 20% ethyl acetate-cyclohexane, collecting 400 ml. fractions. Fractions 38–52 crystallized from methanol to give 2 g. of the ethyl ester of 2,3-bis(p-methoxyphenyl)indole-5-carboxylic acid which after a second recrystallization from methanol had a melting point of 202–203° C.

U.V.: λ_{max} 238.5 (16,000); 271 (50,500); sh. 335 (9,150).

(C) 2.3 · bis(p-methoxyphenyl)indole-5-carboxylic acid (as acetone solvate) from 2-hydroxyethyl-2,3-bis(p-methoxyphenyl)indole-5-carboxylate.—A mixture of 2-hydroxyethyl 2.3 · bis(p-methoxyphenyl)indole-5-carboxylate (Example 2A), 20 g. of potassium hydroxide, 80 ml. of water, and 200 ml. of ethanol was refluxed for 18 hours. The ethanol was evaporated. A solution of the residue in 500 ml. of water was extracted with ether. The aqueous layer was cooled in an ice bath and acidified with concentrated hydrochloric acid. The solid which separated was collected by filtration, washed with water, crystallized from aqueous acetone and dried giving 9 g. (79% yield) of buff needles, melting point 295–298° C. (dec.). Recrystallization from acetone-Skellysolve B hexanes afforded buff needles of 2,3-bis(p-methoxyphenyl)indole-5-carboxylic acid of melting point 297–298° C. (dec.).

U.V.: λ_{max} 269 (50,400); sh. 381 (12,500); sh. 335 (9,650).

Analysis.—Calcd. for C_{21}H_{18}NO_{4}: C, 78.94; H, 5.41; N, 2.51. Found (percent): C, 78.28; H, 5.41; N, 2.46.

**EXAMPLE 3**

5-acetyl-2,3-bis(p-methoxyphenyl)indole

A mixture of 1.0 g. of 2,3-bis(p-methoxyphenyl)indole, 5-carboxylic acid and 10 ml. of thionyl chloride in 25 ml. of benzene was heated at reflux for 1 hour. The resulting intensely yellow solution was taken to dryness to give the acid chloride, 2,3-bis(p-methoxyphenyl)indole-5-carboxylic acid, max. 1760 cm⁻¹.

To a well stirred suspension of 1.80 g. of cadmium chloride in 20 ml. of ether there was added a solution of 6 ml. of 3 M ethereal magnesium bromide in 50 ml. of ether. The suspension was then cooled in ice and treated with a solution of the 2,3-bis(p-methoxyphenyl)indole-5-carboxylic acid in 25 ml. of ether. Following 4 hours heating under reflux, the mixture was again cooled in ice and treated with 50 ml. of 2.5 N hydrochloric acid. Methylenedie chloride was added and the organic layer washed in turn with water, normal aqueous sodium hydroxide solution and again water. The solid which remained when the organic layer was taken to dryness was chromatographed over Florisil (anhydrous magnesium silicate) (elution with 8% acetone). The crystalline fractions were combined and recrystallized twice from ethyl acetate. There was obtained 0.25 g. of 5-acetyl-2,3-bis(p-methoxyphenyl)indole of melting point 222–223° C.

U.V.: λ_{min} 1660 cm⁻¹; λ_{max} 241 (15,300), 284 (50,000), 355 (4,900).

Analysis.—Calcd. for C_{21}H_{18}NO_{4}: C, 77.60; H, 5.70; N, 3.77. Found (percent): C, 77.25; H, 5.88; N, 3.95.

**EXAMPLE 4**

5-propionyl-2,3-bis(p-methoxyphenyl)indole

In the manner given in Example 3, a solution of ethereal ethyl magnesium bromide and cadmium chloride was treated with 2,3-bis(p-methoxyphenyl)indole-5-carboxylic acid and then with aqueous hydrochloric acid to give 5-propionyl-2,3-bis(p-methoxyphenyl)indole.

**EXAMPLE 5**

5-butyryl-2,3-bis(p-methoxyphenyl)indole

In the manner given in Example 3, a solution of ethereal propyl magnesium bromide and cadmium chloride was treated with 2,3-bis(p-methoxyphenyl)indole-5-carboxylic acid and then with aqueous hydrochloric acid to give 5-butyryl-2,3-bis(p-methoxyphenyl)indole.

**EXAMPLE 6**

5-isobutyryl-2,3-bis(p-methoxyphenyl)indole

In the manner given in Example 3, a solution of ethereal isopropyl magnesium bromide and cadmium chloride was treated with 2,3-bis(p-methoxyphenyl)indole-5-carboxylic acid and then with aqueous hydrochloric acid to give 5-isobutyryl-2,3-bis(p-methoxyphenyl)indole.

**EXAMPLE 7**

5-formyl-2,3-bis(p-methoxyphenyl)indole

To a solution of 5 gm. of 2,3-bis(p-methoxyphenyl)indole-5-carboxyl chloride in dry xylool was added 1 gm. of 5% palladium-on-carbon catalyst. The mixture was hydrogenated for 4 hours at the reflux temperature. After cooling, the mixture was filtered, aqueous sodium bisulfite solution was added, the mixture was shaken and then allowed to settle overnight. The bisulfite complex was recovered by filtration, washed with ether and decomposed with aqueous sodium carbonate. The aqueous mixture was extracted twice with methylene chloride, the methylene chloride extracts washed repeatedly with water and evaporated. The resulting residue was recrystallized twice from ethanol to give 5-formyl-2,3-bis(p-methoxyphenyl)indole.

**EXAMPLE 8**

1-methyl-5-acetyl-2,3-bis(p-methoxyphenyl)indole

Sodium hydride (0.46 g. of a 53% dispersion in mineral oil; 0.01 mole) was added to a nitrogen atmosphere to a solution of 0.01 mole of 5-acetyl-2,3-bis(p-methoxyphenyl)indole in 50 ml. of dimethylformamide. After 2 hours, 1 ml. of methyl iodide was added and the mixture stirred for 20 hours overnight. The reaction mixture was then evaporated in vacuo on a steam bath to give a residue. This residue was crystallized from ethanol to give 1-methyl-5-acetyl-2,3-bis(p-methoxyphenyl)indole.

**EXAMPLE 9**

1-ethyl-5-acetyl-2,3-bis(p-methoxyphenyl)indole

In the manner given in Example 8 sodium hydride in mineral oil was added to 5-acetyl-2,3-bis(p-methoxyphenyl)indole and thereto was added ethyl iodide to give 1-ethyl-5-acetyl-2,3-bis(p-methoxyphenyl)indole.

**EXAMPLE 10**

1-propyl-5-acetyl-2,3-bis(p-methoxyphenyl)indole

In the manner given in Example 8 sodium hydride in mineral oil was added to 5-acetyl-2,3-bis(p-methoxyphenyl)indole and thereto was added propyl chloride to give 1-propyl-5-acetyl-2,3-bis(p-methoxyphenyl)indole.

**EXAMPLE 11**

1-butyl-5-acetyl-2,3-bis(p-methoxyphenyl)indole

In the manner given in Example 8 sodium hydride in mineral oil was added to 5-acetyl-2,3-bis(p-methoxyphenyl)indole and thereto was added butyl bromide to give 1-butyl-5-acetyl-2,3-bis(p-methoxyphenyl)indole.
EXAMPLE 12

1-ethyl-5-formyl-2,3-bis(p-methoxyphenyl)indole

In the manner given in Example 8 sodium hydride in mineral oil was added to 5-formyl-2,3-bis(p-methoxyphenyl)indole and thereto was added ethyl iodide to give 1-ethyl-5-formyl-2,3-bis(p-methoxyphenyl)indole.

EXAMPLE 13

1-isopropyl-5-propionyl-2,3-bis(p-methoxyphenyl)indole

In the manner given in Example 8 sodium hydride in mineral oil was added to 5-propionyl-2,3-bis(p-methoxyphenyl)indole and thereto was added isopropyl iodide to give 1-isopropyl-5-propionyl-2,3-bis(p-methoxyphenyl)indole.

EXAMPLE 14

1-isobutyl-5-butyryl-2,3-bis(p-methoxyphenyl)indole

In the manner given in Example 8 sodium hydride in mineral oil was added to 5-butyryl-2,3-bis(p-methoxyphenyl)indole and thereto was added isobutyl chloride to give 1-isobutyl-5-butyryl-2,3-bis(p-methoxyphenyl)indole.

EXAMPLE 15

1-methyl-5-isobutyl-2,3-bis(p-methoxyphenyl)indole

In the manner given in Example 8 sodium hydride in mineral oil was added to 5-isobutyl-2,3-bis(p-methoxyphenyl)indole and thereto was added methyl iodide to give 1-methyl-5-isobutyl-2,3-bis(p-methoxyphenyl)indole.

In the manner given in Example 8 sodium hydride in mineral oil was added to other 5-acetyl-2,3-bis(p-methoxyphenyl)indole and thereto was added an alkyl halide of the formula Alk X, wherein Alk is an alkyl radical of 1 to 4 carbon atoms, inclusive and X is selected from the group consisting of chlorine, bromine and iodine to give 1-alkyl-5-acetyl-2,3-bis(p-methoxyphenyl)indole.

Representative 1-alkyl-5-acetyl-2,3-bis(p-methoxyphenyl)indoles thus produced include:

1-methyl-5-formyl-2,3-bis(p-methoxyphenyl)indole;
1-propyl-5-formyl-2,3-bis(p-methoxyphenyl)indole;
1-isopropyl-5-formyl-2,3-bis(p-methoxyphenyl)indole;
1-butyl-5-formyl-2,3-bis(p-methoxyphenyl)indole;
1-isobutyl-5-formyl-2,3-bis(p-methoxyphenyl)indole;
1-isopropyl-5-acetyl-2,3-bis(p-methoxyphenyl)indole;
1-isobutyl-5-acetyl-2,3-bis(p-methoxyphenyl)indole;
1-methyl-5-propionyl-2,3-bis(p-methoxyphenyl)indole;
1-ethyl-5-propionyl-2,3-bis(p-methoxyphenyl)indole;
1-butyl-5-propionyl-2,3-bis(p-methoxyphenyl)indole;
1-methyl-5-butyryl-2,3-bis(p-methoxyphenyl)indole;
1-ethyl-5-butyryl-2,3-bis(p-methoxyphenyl)indole;
1-methyl-5-butyryl-2,3-bis(p-methoxyphenyl)indole;
1-ethyl-5-butyl-2,3-bis(p-methoxyphenyl)indole;
1-propyl-5-isobutyl-2,3-bis(p-methoxyphenyl)indole;
1-isopropyl-5-isobutyl-2,3-bis(p-methoxyphenyl)indole;
1-methyl-5-isononyl-2,3-bis(p-methoxyphenyl)indole;
and the like.

EXAMPLE 16

1,5-diacetyl-2,3-bis(p-methoxyphenyl)indole

Sodium hydride (0.46 g. of a 53% dispersion in mineral oil 0.01 mole) was added in a nitrogen atmosphere to a solution of 0.01 mole of 5-acetyl-2,3-bis(p-methoxyphenyl)indole in 50 mL of dimethylformamide. After 2 hours, 1 mL of acetyl chloride was added and the mixture stirred for 20 hours overnight. The reaction mixture was then evaporated in vacuo on a steam bath to give a residue. This residue was crystallized from chloroform-ether to give 1,5-diacetyl-2,3-bis(p-methoxyphenyl)indole.

EXAMPLE 17

1-acetyl-5-formyl-2,3-bis(p-methoxyphenyl)indole

In the manner given in Example 16 sodium hydride in mineral oil was added to 5-formyl-2,3-bis(p-methoxyphenyl)indole and thereto was added acetyl chloride to give 1-acetyl-5-formyl-2,3-bis(p-methoxyphenyl)indole.

EXAMPLE 18

1-propionyl-5-acetyl-2,3-bis(p-methoxyphenyl)indole

In the manner given in Example 16 sodium hydride in mineral oil was added to 5-acetyl-2,3-bis(p-methoxyphenyl)indole and thereto was added propionyl chloride to give 1-propionyl-5-acetyl-2,3-bis(p-methoxyphenyl)indole.

EXAMPLE 19

1-butyryl-5-acetyl-2,3-bis(p-methoxyphenyl)indole

In the manner given in Example 16 sodium hydride in mineral oil was added to 5-acetyl-2,3-bis(p-methoxyphenyl)indole and thereto was added butyryl bromide to give 1-butyryl-5-acetyl-2,3-bis(p-methoxyphenyl)indole.

EXAMPLE 20

1-butyryl-5-propionyl-2,3-bis(p-methoxyphenyl)indole

In the manner given in Example 8 sodium hydride in mineral oil was added to 5-propionyl-2,3-bis(p-methoxyphenyl)indole and thereto was added butyryl chloride to give 1-butyryl-5-propionyl-2,3-bis(p-methoxyphenyl)indole.

EXAMPLE 21

1-propionyl-5-butyryl-2,3-bis(p-methoxyphenyl)indole

In the manner given in Example 16 sodium hydride in mineral oil was added to 5-butyryl-2,3-bis(p-methoxyphenyl)indole and thereto was added propionyl bromide to give 1-propionyl-5-butyryl-2,3-bis(p-methoxyphenyl)indole.

EXAMPLE 22

G-propionyl-5-isobutyl-2,3-bis(p-methoxyphenyl)indole

In the manner given in Example 16 sodium hydride in mineral oil was added to 5-isobutyl-2,3-bis(p-methoxyphenyl)indole and thereto was added propionyl bromide to give 1-propionyl-5-isobutyl-2,3-bis(p-methoxyphenyl)indole.

In the manner given in the before going examples other 1- acetyl-5-acetyl-2,3-bis(p-methoxyphenyl)indoles are produced by reacting a 5- acetyl-2,3-bis(p-methoxyphenyl)indole with sodium hydride and then with an acid chloride or acid bromide. Representative 1-acetyl-5-acetyl-2,3-bis(p-methoxyphenyl)indoles, thus produced, include:

1-isobutyl-5-formyl-2,3-bis(p-methoxyphenyl)indole;
1-butyryl-5-formyl-2,3-bis(p-methoxyphenyl)indole;
1-propionyl-5-formyl-2,3-bis(p-methoxyphenyl)indole;
1-acetyl-5-propionyl-2,3-bis(p-methoxyphenyl)indole;
1,5-dipropionyl-2,3-bis(p-methoxyphenyl)indole;
1-acetyl-5-propionyl-2,3-bis(p-methoxyphenyl)indole;
1,5-dibutyryl-2,3-bis(p-methoxyphenyl)indole;
1,5-disobutyryl-2,3-bis(p-methoxyphenyl)indole;
1-isobutyl-5-propionoyl-2,3-bis(p-methoxyphenyl)indole;
1-acetyl-5-butyl-2,3-bis(p-methoxyphenyl)indole;
and the like.

I claim:
1. 2 - hydroxyethyl 2,3-bis(p-methoxyphenyl)indole-5-carboxylate.
2. 5-carboxy-2,3-bis(p-methoxyphenyl)indole.
3. 2,3 - bis(p-methoxyphenyl)indole-5-carboxylic acid.

No references cited.

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