

PATENT SPECIFICATION

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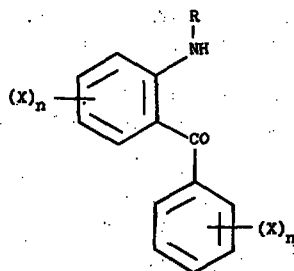
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(54) PREPARATION OF SUBSTITUTED AMINOBENZOPHENONES

(71) We, RANBAXY LABORATORIES LIMITED, of Okhla, New Delhi—110020, India, an Indian Company, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a novel process for the manufacture of substituted aminobenzophenones, more particularly ortho alkylamino benzophenones of the following general formula:



in which R is a C₁₋₈ alkyl group, or an aralkyl radical optionally substituted in the aromatic nucleus, examples of substituents being C₁₋₈ alkyl, F, Cl, Br and CF₃; X is Cl, CF₃, F or Br and n is zero or an integer from 1 to 5, depending on the availability of the substitutive positions in the phenyl nuclei.

The compounds of formula I of most interest in the invention bear either a chloro or trifluoromethyl radical at the 5-position and a C₁₋₈ alkyl or aralkyl (e.g. benzyl) radical on the nitrogen atom of the amino group on the 2-position of the benzophenone molecule. Such a compound is 2-methylamino-5-chloro-benzophenone.

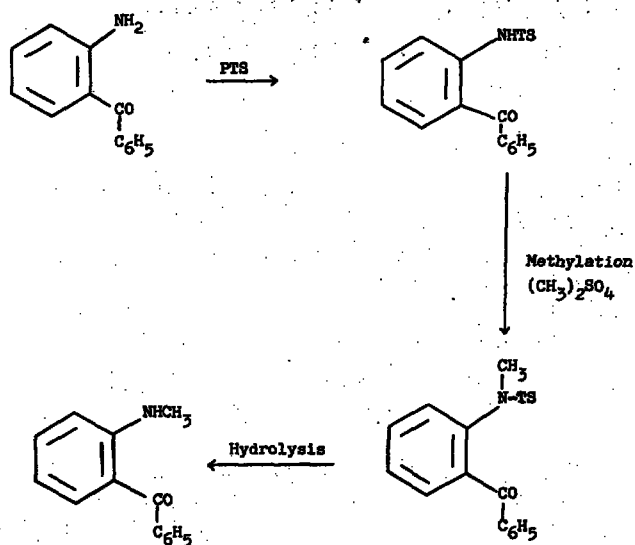
The methods hitherto employed for the manufacture of ortho alkylamino benzophenones almost invariably use o-amino benzophenones as the starting material. In one of the known methods the o-amino group is protected by reaction with benzene sulfonyl chloride or paratoluene sulfonyl chloride (PTS) and the sulfonamide obtained is alkylated with an alkylating agent. Removal of the protective group from the protected o-alkylamino group by hydrolysis gives o-alkylamino benzophenones. This method may be represented by the following reaction scheme:

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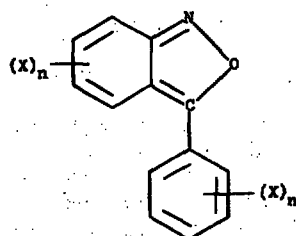
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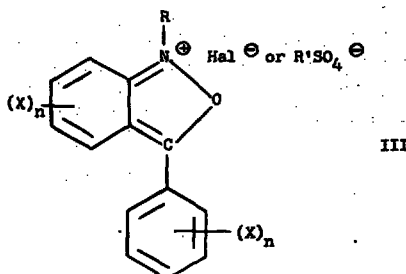
The above method suffers from two major drawbacks, i.e. it involves isolation of several intermediates, which is both cumbersome and expensive, and the yield of the final product is very poor.

Another known method employs direct alkylation of *o*-aminobenzophenones by methyl paratoluene sulphonate. In this case the yields and purity of the product are far from satisfactory.

According to the present invention a process for the manufacture of compounds of formula I which comprises reacting a compound of the following formula:



wherein X and n are as defined above, with alkylating or aralkylating agent to produce a quaternary salt of the following formula:

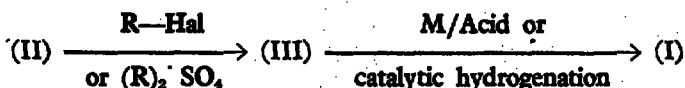


wherein R, X and n are as defined above and R' is C_{1-6} alkyl and Hal is halogen, and reducing the quaternary salt to obtain a compound of formula I.

The process according to the invention uses substituted anthranils (II) as the starting material and these may readily be prepared by reaction of aromatic nitro compounds optionally substituted with Cl, Br, F or CF_3 , with benzyl cyanide, optionally substituted with Cl, Br, F or CF_3 groups in strongly basic alcoholic (e.g. methanolic) solution. The anthranils (II), by reaction with alkylating or aralkylating agents

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e.g. alkyl halides, dialkyl sulphates, and aralkyl halides can be converted to the quaternary salts (III) in almost quantitative yields. The optimum reaction conditions vary with the nature of the alkylating or aralkylating agent, e.g. the halide, used. The alkylation (or aralkylation, as the case may be) of the anthranil derivatives (II) is found to proceed satisfactorily between 30° and 110°C. The quaternary salts (III) thus obtained are usually coloured, crystalline solids and insoluble in non-polar solvents like benzene or toluene. These salts owing to their insolubility separate from the reaction mixture in almost pure condition. Chloroform may also be used as solvent during the alkylation or aralkylation. The quaternary salts (III) may be reduced, by techniques well known in the art, to produce benzophenones (I) in high yield and purity. Reduction of the quaternary salts may be effected by the use of conventional metal-acid mixtures, such as, for example, Sn/HCl, Fe/HCl, Zn/HAc or Fe/HAc or by catalytic hydrogenation wherein supported palladium or platinum or Raney nickel is used as the catalyst. The above sequence of reactions may be schematically represented as follows:—



where R is as defined above and M is a metal such as Sn, Fe, or Zn.

The process of the present invention has the following main advantages. First, the products can be prepared in high yields. Secondly, since the intermediate quaternary salt (III) is virtually insoluble in non-polar organic solvents, it separates without much difficulty from the reaction mixture in very pure form, uncontaminated with the starting material and reduction of (III) leads to the desired products having a very high degree of purity. Thirdly, the present process avoids the need for isolation of intermediates, thereby avoiding any losses during such isolation.

The compounds (I) are very important, and are particularly useful in the manufacture of a number of pharmaceutical products including "Diazepam" and related benzodiazepine derivatives.

The following Examples illustrate the invention.

EXAMPLE 1

a) Preparation of N-methyl-3-phenyl-5-chloro anthranil methosulfate

A mixture of 3-phenyl-5-chloroanthranil (115 gm), dimethyl sulphate (126 gm) and toluene (200 ml) was heated together with stirring at 110°C for two hours. After almost one hour the separation of the quaternary salt started. The mixture after reaction was cooled to 10°C and the separated solid was filtered off. The pure yellow crystalline solid (154 gm) which crystallised out had M.P. 173—174°C.

b) Preparation of 2-methyl amino-5-chlorobenzophenone

A solution of N-methyl-3-phenyl-5-chloro anthranil methosulphate (202 gm) in glacial acetic acid (2.00 lit.) was heated to reflux and treated with iron powder (182 gm.) in 5 gm. lots at a time, during the course of 2-1/2 hours. Water (342 ml) was simultaneously dropped into the stirred reaction mixture during the same period. The mixture was refluxed with stirring for an additional 30 minutes and filtered hot. The filtrate was poured into water (10 lit.) containing ice (2.5 kg.) with stirring. The precipitated 2-methyl-amino-5-chlorobenzophenone was filtered off, washed with water and dried in vacuum at 60°C. The yield of the dry 2-methyl amino-5-chloro benzophenone was 110 gm. The product was obtained as a bright yellow powder, M.P. 91—92°C. The product gave a single spot on TLC. (Silica gel plates with benzene as mobile phase).

EXAMPLE 2

Preparation of 2-methyl amino-5-chlorobenzophenone by catalytic hydrogenation

Preparation of 2-methyl amino-5-chlorobenzophenone by catalytic hydrogenation
To a solution of N-methyl-3-phenyl-5-chloro-anthranil methosulphate (10 gm.) [obtained as in Example 1(a)] dissolved in acetic acid (100 ml) was added (0.5 gm.) of 5% palladium on charcoal. The stirred solution was hydrogenated at atmospheric pressure and room temperature by passing hydrogen gas therethrough. After 30 minutes, the catalyst was filtered off and the filtrate poured into ice and water. 2-Methyl-amino-5-chlorobenzophenone precipitated as a bright yellow solid which was filtered, washed and dried. The yield of the dry product was 5.0 gm.

EXAMPLE 3

a) Preparation of N-ethyl-3-phenyl-5-chloroanthranil-ethosulphate

A mixture of 3-phenyl-5-chloroanthranil (5.7 gms), diethyl sulfate (7 gms) and toluene (20 ml) were heated together with stirring at 110°C for 3 hours. The reaction mixture was cooled and the solid separated filtered off to give the ethosulphate as yellow crystalline solid (4 gms.), M.P. 240°C (with decomposition).

b) Preparation of 2-ethyl-amino-5-chloro benzophenone

A solution of N-ethyl-3-phenyl-5-chloroanthranil ethosulphate (2 gms) in glacial acetic acid (10 ml) was heated to reflux, and iron powder (2 gms), added in small lots at a time during the course of 2 hours. Water (3 ml) was simultaneously dropped into the reaction vessel. The mixture was refluxed for 1 hour and filtered hot. The dilution of the filtrate with water yielded N-ethyl-amino-5-chlorobenzophenone which was crystallised from petroleum ether, giving yellow crystals (1.2 gm), M.P. 74—76°C.

EXAMPLE 4

a) Preparation of N-methyl-3-phenyl-5-bromo anthranil methosulphate

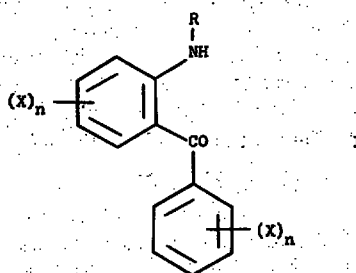
A solution of 3-phenyl-5-bromo anthranil (5 gms) in benzene (20 ml) was treated with dimethyl sulphate (7 ml) and the mixture refluxed for 5-1/2 hours. The metho sulphate separated on cooling (4.5 gms) as yellow solid. The product had M.P. 130—132°C.

b) Preparation of 2-methylamino-5-bromo benzophenone

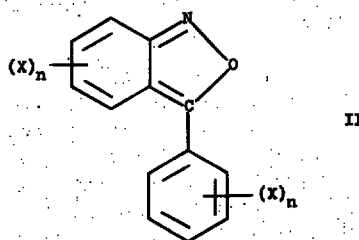
A mixture of N-methyl-3-phenyl-5-bromo anthranil metho sulphate (2 gms) in acetic acid (20 ml) and iron powder (3 gms) was heated under reflux for one hour. Water (5 ml) is gradually dropped into the reaction mixture during the same period. After the completion of water addition, the mixture is refluxed for 30 more minutes and filtered hot. The filtrate was poured with stirring into ice cold water (200 ml). The solid separated was filtered off to give 2-methylamino-5-bromo benzophenone as a yellow crystalline solid (1.8 gms), M.P. 91—94°C.

WHAT WE CLAIM IS:—

1. A process for the manufacture of substituted amino benzophenones of the general formula:



in which R is a C₁₋₆ alkyl group, or an aralkyl radical, optionally substituted in the aromatic nucleus; X is Cl, CF₃, F or Br and n is zero or an integer from 1 to 5, depending on the availability of the substitutive positions in the phenyl nuclei, which comprises reacting a compound of the formula:



in which X and n are as defined above, with an alkylating or aralkylating agent to produce a quaternary salt of the formula:

EXAMPLE 3

a) Preparation of N-ethyl-3-phenyl-5-chloroanthranil-ethosulphate

A mixture of 3-phenyl-5-chloroanthranil (5.7 gms), diethyl sulfate (7 gms) and toluene (20 ml) were heated together with stirring at 110°C for 3 hours. The reaction mixture was cooled and the solid separated filtered off to give the ethosulphate as yellow crystalline solid (4 gms.), M.P. 240°C (with decomposition).

b) Preparation of 2-ethyl-amino-5-chloro benzophenone

A solution of N-ethyl-3-phenyl-5-chloroanthranil ethosulphate (2 gms) in glacial acetic acid (10 ml) was heated to reflux, and iron powder (2 gms), added in small lots at a time during the course of 2 hours. Water (3 ml) was simultaneously dropped into the reaction vessel. The mixture was refluxed for 1 hour and filtered hot. The dilution of the filtrate with water yielded N-ethyl-amino-5-chlorobenzophenone which was crystallised from petroleum ether, giving yellow crystals (1.2 gm), M.P. 74—76°C.

EXAMPLE 4

a) Preparation of N-methyl-3-phenyl-5-bromo anthranil methosulphate

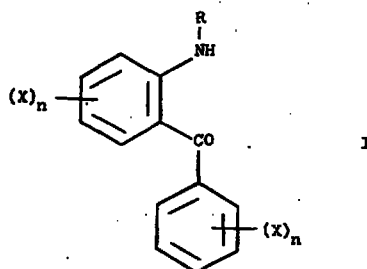
A solution of 3-phenyl-5-bromo anthranil (5 gms) in benzene (20 ml) was treated with dimethyl sulphate (7 ml) and the mixture refluxed for 5-1/2 hours. The metho sulphate separated on cooling (4.5 gms) as yellow solid. The product had M.P. 130—132°C.

b) Preparation of 2-methylamino-5-bromo benzophenone

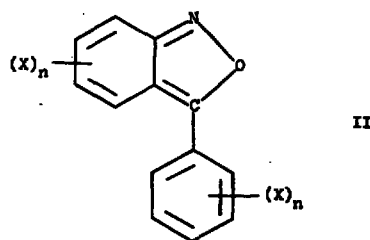
A mixture of N-methyl-3-phenyl-5-bromo anthranil metho sulphate (2 gms) in acetic acid (20 ml) and iron powder (3 gms) was heated under reflux for one hour. Water (5 ml) is gradually dropped into the reaction mixture during the same period. After the completion of water addition, the mixture is refluxed for 30 more minutes and filtered hot. The filtrate was poured with stirring into ice cold water (200 ml). The solid separated was filtered off to give 2-methylamino-5-bromo benzophenone as a yellow crystalline solid (1.8 gms), M.P. 91—94°C.

WHAT WE CLAIM IS:—

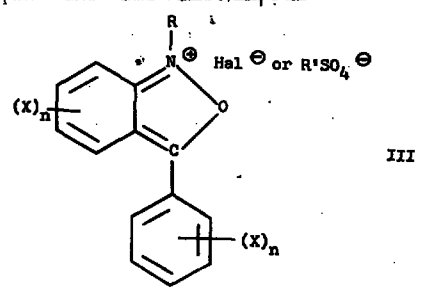
1. A process for the manufacture of substituted amino benzophenones of the general formula:



in which R is a C₁₋₆ alkyl group, or an aralkyl radical, optionally substituted in the aromatic nucleus; X is Cl, CF₃, F or Br and n is zero or an integer from 1 to 5, depending on the availability of the substitutive positions in the phenyl nuclei, which comprises reacting a compound of the formula:



in which X and n are as defined above, with an alkylating or aralkylating agent to produce a quaternary salt of the formula:



in which R, X and n are as defined above, R' is C₁₋₈ alkyl and Hal is halogen, and reducing the quaternary salt to obtain a compound of formula I.

5 2. A process as claimed in claim 1, wherein R is C₁₋₈ alkyl, benzyl or benzyl having one or more substituents in the aromatic nucleus chosen from C₁₋₈ alkyl, F, Cl, Br or CF₃. 5

3. A process as claimed in claim 1, wherein the compound of formula II is reacted with an alkylating agent.

10 4. A process as claimed in claim 3, wherein the alkylating agent is methyl iodide or dimethyl sulphate. 10

5. A process as claimed in any preceding claim, wherein the reaction with the alkylating or aralkylating agent is carried out in a non-polar solvent.

6. A process as claimed in claim 5, wherein the solvent is benzene or toluene.

15 7. A process as claimed in any of claims 1 to 4, wherein the alkylation or aralkylation is carried out in chloroform as solvent. 15

8. A process as claimed in any preceding claim, wherein the reaction with the alkylating or aralkylating agent is carried out at a temperature of between 30°C and 110°C.

20 9. A process as claimed in any preceding claim, wherein the quaternary salt is produced by reacting the salt with a metal/acid mixture selected from Sn/HCl, Fe/HCl, Zn/HAc, and Fe/HAc. 20

10. A process as claimed in any of claims 1 to 8, wherein the quaternary salt is reduced by catalytic hydrogenation using a supported palladium or platinum catalyst or Raney nickel.

25 11. A process as claimed in claim 1, substantially as hereinbefore described with reference to the Examples. 25

12. A substituted aminobenzophenone when made by a process as claimed in any preceding claim.

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