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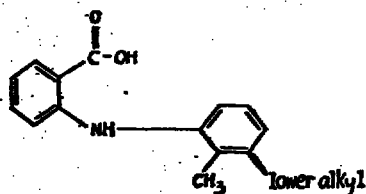
International Classification:—C07c.

COMPLETE SPECIFICATION

Anthranilic Acid Derivatives and methods for producing same

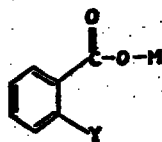
We, PARKE, DAVIS & COMPANY, a corporation organized under the laws of the State of Michigan, United States of America, of Joseph Campau at the River, Detroit, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel anthranilic acids having useful pharmacodynamic properties and to methods for producing same. More particularly, the present invention relates to anthranilic acids and salts thereof, said anthranilic acids having in their free acid the formula

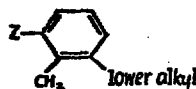


The word "lower" when used to qualify a radical is to mean that the radical contains not more than four carbon atoms. The compounds wherein "lower alkyl" is a methyl or ethyl group possess exceptionally high activity and are the preferred compounds of the invention.

In accordance with the invention, the novel compounds of the above formula and their salts are produced by condensing a benzoic acid derivative of the formula



with a compound of the formula



and, if desired, thereafter converting the condensation product either to the free acid or to a salt, where M represents hydrogen or a metal (preferably an alkali metal), Y and Z represent —NH₂ or halogen, Z being —NH₂ when Y is halogen and Z being halogen when Y is —NH₂. Bromine is the preferred halogen for Z or Y. The reaction is preferably carried out in the presence of a copper-containing catalyst and a proton acceptor, and the anthranilic acid compound so obtained is thereafter converted by acidification to the free acid. In carrying out this condensation it is generally satisfactory to employ substantially equivalent quantities of the reactants in the presence of a suitable solvent. Some examples of such solvents are N,N-dimethylformamide, diethylene glycol dimethyl ether, dimethyl sulfoxide, nitrobenzene, and aliphatic alcohols such as n-butanol, amyl alcohol and isoamyl alcohol. Preferred solvents are N,N-dimethylformamide and diethylene glycol dimethyl ether. In general, the reaction is favored by temperatures in excess of 75°C. and is preferably carried out at a temperature between 100°C. and 200°C.

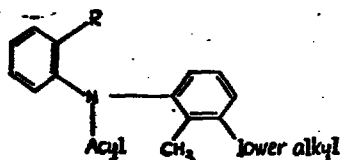
In an advantageous process for producing N-(2,3-dimethylphenyl) anthranilic acid, which is a preferred compound of the invention, an o-halobenzoic acid or a metal salt thereof is condensed with 2,3-dimethylaniline in the presence of a copper containing catalyst and a proton acceptor and the N-(2,3-dimethylphenyl)-anthranilic acid compound so produced converted by acidification to the free acid.

Some examples of the copper-containing catalysts which can be used in carrying out the process are various forms of mechanically divided or chemically precipitated metallic copper such as powdered copper or spongy copper and various copper-containing compounds such as cuprous bromide, cuprous chloride, cupric acetate, cupric carbonate, cupric oxide and cupric sulfate. Cupric bromide and cupric acetate are preferred catalysts.

The quantity of the proton acceptor employed in the reaction can be varied within wide limits. In general, sufficient should be used to bind the benzoic acid reactant and the hydrohalic acid formed in the course of the reaction. Some of the proton acceptors which can be used when the benzoic acid derivative is employed in free acid form are alkali metal carbonates, preferably potassium carbonate; cupric carbonate and cuprous carbonate. When an alkali metal salt, preferably the potassium salt, of the benzoic acid reactant is employed, the following substances can be used as the proton acceptor: calcium hydride, alkali metal carbonates such as potassium carbonate and tertiary organic amines such as N-ethylmorpholine. If desired, two or more equivalents of the amine reactant can be used, in which case one equivalent takes part in the condensation and the remainder acts as the proton acceptor.

The benzoic acid reactant is advantageously added to the reaction mixture in the form of its preformed alkali metal salt, preferably the potassium salt. Alternatively, the potassium salt of the benzoic acid reactant can be conveniently prepared *in situ* in a very finely divided condition by adding potassium carbonate to a boiling solution of the free acid form of the corresponding benzoic acid derivative in the solvent employed in the reaction. In the latter case, it is often advantageous to remove most of the water formed in the neutralization by distilling some of the solvent prior to the addition of the catalyst and other reactant.

The compounds of the invention can also be prepared by hydrolysing an N-acylated diphenylamine compound of formula



and, if desired, thereafter converting the hydrolysis product to either the free acid or to a salt; where Acyl represents an acyl radical, preferably benzoyl, and R is a carboxy group (either in free acid or salt form) or a group hydrolyzable to a carboxy group

such as a cyano, carboalkoxy, carboaryloxy, carboarylalkoxy, carbamide or carbonyl halide group. The precise nature of the acyl group and the group hydrolyzable to a carboxy group is not critical because during the process the acyl group is removed and the hydrolyzable group is converted to a carboxyl group. Therefore, if desired, the acyl group and, in the appropriate cases, the group hydrolyzable to a carboxy group may contain one or more substituents such as lower alkyl, lower alkoxy, halogen, nitro, carboxy and carboalkoxy groups and as used herein the terms "acyl" and "group hydrolyzable to a carboxy group" will be understood to include the substituted as well as the unsubstituted radicals. The hydrolysis can be carried out either in an acidic or alkaline medium. An alkaline medium is preferred, in which case the salt of the anthranilic acid so obtained may thereafter be converted to the free acid by acidification. The hydrolysis in an alkaline medium can be effected by dissolving the N-acylated diphenylamine compound in a water-miscible, non-reactive organic solvent such as ethanol or methanol, adding a large excess of a concentrated aqueous solution of sodium or potassium hydroxide and allowing the hydrolysis to proceed (with or without stirring) until the reaction is complete. The hydrolysis is favored by temperatures in excess of 75°C. and is preferably effected at temperatures ranging from 75°C. to about 150°C. The hydrolysis not only removes the N-acyl group from the acylated diphenylamine compound but also converts the group hydrolyzable to a carboxy group, if present, to a carboxyl group. When alkaline reaction conditions are used, the anthranilic acid compound is present in the reaction mixture in the form of a carboxylate salt while if acidic conditions are used, it is present as the free acid.

The compounds of the invention possess anti-pyretic, anti-nociceptive and anti-inflammatory activity, have a surprisingly low degree of toxicity and are of value in mitigating the symptoms associated with rheumatic, arthritic and other inflammatory conditions. They are preferably administered by the oral route but can also be administered parenterally. Either the free acids or pharmaceutically-acceptable salts formed with a variety of inorganic and organic bases can be used. Some typical examples of these salts are the sodium, potassium, calcium, ammonium, choline, 2-hydroxyethylamine, bis(2-hydroxyethyl)-amine and tris(2-hydroxyethyl)amine salts. Preferred salts are the pharmaceutically-acceptable salts of an alkali metal, an alkaline earth metal, ammonia, a substituted amine or a quaternary nitrogen compound. Any of the salts or free acids of the invention can be combined with one or more solid or liquid carriers or diluents and made available in various dosage unit forms such as tablets, capsules, powders, aqueous and

non-aqueous suspensions and solutions, or other pharmaceutical forms suitable for oral or parenteral administration.

The invention is illustrated by the following examples:

EXAMPLE 1

A mixture of 800 g. of potassium *o*-bromobenzoate, 1500 ml. of bis(2-methoxyethyl)-ether, 355 g. of *N*-ethylmorpholine, 375 g. of 2,3-dimethylaniline, and 30 g. of cupric acetate is heated gradually with stirring to 140°C. over a period of ninety minutes. The hot reaction mixture is then acidified with 260 ml. of concentrated hydrochloric acid and the acidified mixture divided into two equal portions. One liter of water is added to each portion and the mixtures allowed to cool. The *N*-(2,3-dimethylphenyl)-anthranilic acid which separates upon cooling is collected and recrystallized from bis(2-methoxyethyl)-ether; m.p. 229—230°C. (corr.).

10.0 G. of sodium carbonate is added portion-wise to a suspension of 20.0 g. of *N*-(2,3-dimethylphenyl)-anthranilic acid in 300 ml. of methanol and the mixture heated on a steam bath. The resulting solution is filtered from the excess solid sodium carbonate and the filtrate evaporated to dryness. The sodium salt of *N*-(2,3-dimethylphenyl)-anthranilic acid is ground in a mortar and dried *in vacuo* at 100°C. If desired, the salt may be recrystallized from a small portion of ethanol or water.

The potassium salt can be prepared similarly.

Choline chloride (2.65 g.) dissolved in ethanol is added to an ethanolic solution of 5.0 g. of the sodium salt of *N*-(2,3-dimethylphenyl)-anthranilic acid. The mixture is heated to about 70°C. for five to ten minutes. The sodium chloride which forms in the course of the reaction is removed and the filtrate concentrated *in vacuo* to give a clear oily residue from which the *N*-(2,3-dimethylphenyl)-anthranilic acid choline salt crystallizes on standing.

EXAMPLE 2

A stirred mixture of 35.8 g. of potassium *o*-bromobenzoate, 20.2 g. of 2-methyl-3-ethylaniline, 20 ml. of *N*-ethylmorpholine, 1.5 g. of cupric bromide, and 75 ml. of diethylene glycol dimethyl ether is heated at about 140°C. for one hour. 15 ml. of concentrated hydrochloric acid is added to the hot reaction mixture, the *N*-ethylmorpholine hydrochloride which separates is collected by filtration and 180 ml. of water added portionwise to the hot filtrate. The aqueous solution is then cooled to 0—5°C. The *N*-(2-methyl-3-ethylphenyl)-anthranilic acid which separates is collected by filtration, dried, and recrystallized from diethylene glycol dimethyl ether; m.p. 175—175.5°C.

10 G. of *N*-(2-methyl-3-ethylphenyl)-anthranilic acid and 300 ml. of methanol is warmed on a steam bath while 5.0 g. of sodium carbonate is added in small portions.

The hot solution is filtered and the filtrate evaporated to dryness on a steam bath to obtain the desired sodium salt of *N*-(2-methyl-3-ethylphenyl)-anthranilic acid.

A mixture of 2.65 g. of choline chloride and 5.0 g. of the sodium salt of *N*-(2-methyl-3-ethylphenyl)-anthranilic acid in ethanol is heated to about 70°C. for five to ten minutes. The sodium chloride which forms in the course of the reaction is removed by filtration and the filtrate concentrated *in vacuo* to give a clear oily residue from which the *N*-(2-methyl-3-ethylphenyl)-anthranilic acid choline salt crystallizes on standing.

The 2-methyl-3-ethylaniline used as a starting material in the above procedure can be prepared by reacting 2-iodo-6-nitrotoluene with ethyl iodide in the presence of metallic sodium to obtain 2-nitro-6-ethyltoluene and reducing the nitro group in the latter substance with iron in methanol containing a small amount of concentrated hydrochloric acid.

EXAMPLE 3

A mixture of 45.0 g. of the potassium salt of anthranilic acid, 37.0 g. of 1,2-dimethyl-3-bromobenzene, 4.5 g. of calcium hydride and 4.0 g. of cupric acetate in 100 ml. of dimethyl sulfoxide is heated gradually with stirring to around 150°C. and maintained between 130 and 150°C. for three hours. The reaction mixture is diluted with an equal volume of water, 20 ml. of 2*N* sodium hydroxide is added, and the mixture is extracted with several portions of ether. The aqueous solution is then acidified with concentrated hydrochloric acid and the *N*-(2,3-dimethylphenyl)-anthranilic acid which separates is collected, digested with several portions of boiling water and recrystallized from absolute ethanol; m.p. 229—230°C.

By substituting 49.2 g. of 2-iodo-6-ethyltoluene for the 37.0 g. of 1,2-dimethyl-3-bromobenzene in the above example, *N*-(2-methyl-3-ethylphenyl)-anthranilic acid is obtained.

EXAMPLE 4

A mixture of 25.0 g. of *N*-(2,3-dimethylphenyl)-*N*-benzoylanthranilic acid methyl ester, 250 ml. of ethanol, 10.0 g. of sodium hydroxide and 20.0 ml. of water is refluxed for two hours. 150 ml. of the solvent is distilled from the reaction mixture and a solution of 60.0 g. of sodium hydroxide dissolved in 100 ml. of water is added. The hydrolysis mixture is heated an additional two hours and the remaining ethanol removed by distillation. The aqueous residue is acidified with concentrated hydrochloric acid and cooled. The precipitate which forms on cooling is collected and digested with several portions of boiling water. The residue is dissolved in a minimum quantity of hot bis(2-methoxyethyl)ether and allowed to cool. The *N*-(2,3-dimethylphenyl)-anthranilic acid which separates upon cooling



is collected and dried *in vacuo* at 60°C.; m.p. 229°—230°C.

By substituting 25.0 g. of N - (2 - methyl-3 - ethylphenyl) - N - (p - chlorobenzoyl)-anthranilic acid methyl ester for the 25.0 g. of N - (2,3-dimethylphenyl) - N - benzoyl-anthranilic acid methyl ester in the above procedure, N - (2 - methyl - 3 - ethylphenyl)-anthranilic acid is obtained.

If desired, esters other than the methyl ester can be used in the above procedures. For example, one can use the benzyl ester or the ethyl ester. Additionally, one can employ an N - acyl - N - (2,3 - dimethylphenyl) - anthranilic acid halide as a starting material. Such acid halides can be prepared by reacting an N - acyl - N - (2,3 - dimethylphenyl) - anthranilic acid with a thionyl halide.

N - (2,3 - Dimethylphenyl) - anthranilic acid can also be prepared by using N - pivalyl-N - (2,3 - dimethylphenyl) - anthranilic acid or the methyl ester as starting materials. This is carried out as follows:

1 g. of N-pivalyl-N-(2,3-dimethylphenyl)-anthranilic acid or the methyl ester thereof is heated under reflux overnight in a mixture consisting of 3.5 g. of 85% potassium hydroxide, 2.5 ml. of water and 5 ml. of ethylene glycol. The reaction mixture is diluted with water, extracted with ether and the aqueous solution acidified to obtain the desired N - (2,3 - dimethylphenyl) - anthranilic acid; m.p. 216—224°C. The product after recrystallization from ethanol and extraction with benzene melts at 225.5—227.5°C. Further recrystallization raises the melting point to 229—30°C.

The N - (2,3 - dimethylphenyl) - N-benzoylanthranilic acid methyl ester employed as starting material above can be prepared in the following manner:

A mixture of 32.0 g. of 2',3'-dimethylbenzanilide and 36.0 g. of powdered phosphorus pentachloride is heated on a steam bath for one-half hour. The phosphorus oxychloride which forms in the course of the reaction is removed by evaporation *in vacuo* and the residue treated with petroleum ether (b.p. 60—80°C.; dried over sodium) and the petroleum ether distilled to remove final traces of phosphorus chlorides. The residue is refluxed with about 300 ml. of petroleum ether for thirty minutes and the solution decanted from insoluble material. Evaporation of the petroleum ether solvent *in vacuo* yields the N - (2,3-dimethylphenyl) - benzimidoyl chloride which can be used without further purification.

Methyl salicylate (15.2 g.) and a solution of 24.3 g. of N - (2,3 - dimethylphenyl)-benzimidoyl chloride in dry ether are added in rapid succession to a solution of sodium ethoxide prepared from 2.3 g. of sodium and 200 ml. of absolute ethanol. The reaction mixture is shaken vigorously for thirty minutes

and then allowed to stand at room temperature for forty-eight hours. The solvent is evaporated *in vacuo*, the residue diluted with water and the aqueous mixture extracted with several portions of ether. The ethereal solution is washed successively with aqueous sodium carbonate and water, dried and the ether removed *in vacuo*. The crude imido ester is then heated in a nitrogen atmosphere at 225—245°C. for about ninety minutes and the resulting product dissolved in ethanol and treated with activated charcoal. The N-(2,3-dimethylphenyl) - N - benzoylanthranilic acid methyl ester may be utilized without further purification.

The N - pivalyl - N - (2,3 - dimethylphenyl) - anthranilic acid and the methyl ester thereof used as starting materials above can be prepared as follows:

26.6 g. of pivalyl chloride is added to 24 g. of 2,3-dimethylaniline in 25 ml. of pyridine over a period of five minutes with occasional cooling. The temperature at the end of the addition is about 75°C. The reaction mixture is allowed to stand for 20 minutes, the solid product broken up, washed with water, and the N-pivalyl-2,3-dimethylaniline collected; m.p. 120—1°C. The product is recrystallized from ethanol; m.p. 121.5—122°C.

10 G. of N-pivalyl-2,3-dimethylaniline in 20 ml. of thionyl chloride is warmed at 60°C. until gas evolution is almost complete (55 minutes). The mixture is concentrated under reduced pressure at 50°C., the residue diluted with benzene and the benzene distilled. The residual oil which is N-(2,3-dimethylphenyl)-pivalimidoyl chloride is added to 0.0506 mole of the sodium salt of methyl salicylate in 25 ml. of diethylene glycol dimethyl ether. The reaction mixture is kept at 55°C. for one hour and allowed to stand overnight at room temperature. The mixture is diluted with 400 ml. of petroleum ether, the organic layer washed six times with a total of 500 ml. of ice water and once with sodium chloride solution. The organic layer is dried over sodium sulfate and the solvents evaporated to obtain the desired pivalimidoic acid ester. The pivalimidoic acid ester is heated at 200°C. for 30 minutes to obtain N-pivalyl-N-(2,3-dimethylphenyl)-anthranilic acid methyl ester. The free acid is obtained by heating 15 g. of the ester for 4 hours under reflux with 7 g. of 50% sodium hydroxide in 220 ml. of 90% ethanol. The solution is concentrated to dryness, diluted with 300 ml. of water and extracted with ether. The aqueous phase is acidified and the N-pivalyl-N-(2,3-dimethylphenyl)-anthranilic acid collected and recrystallized from aqueous ethanol; m.p. 158.5—161°C.

EXAMPLE 5

N - benzoyl - 2 - cyano - 2',3' - dimethyldiphenylamine (17.8 g.) is suspended in 125 ml. of 50% (v/v) sulfuric acid and the mix-

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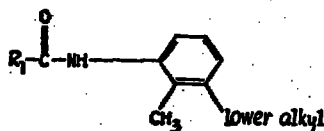
ture refluxed for three hours. The mixture is pooled and the sulfuric acid solution decanted from the tar present into one liter of cold water. The diamide which precipitates is then further hydrolyzed by refluxing for three hours in 270 ml. ethanol containing 95 g. 50% sodium hydroxide. The ethanol is partially removed under reduced pressure, the solution diluted with water and acidified. The precipitated N - (2,3 - dimethylphenyl) - anthranilic acid is collected, washed with hot water and recrystallized from ethanol; m.p. 229—30°C.

If desired, the hydrolysis can be carried out in one step by refluxing 43.5 g. of N-benzoyl-2-cyano-2',3'-dimethyldiphenylamine in 172 g. of 50% sodium hydroxide and 515 ml. of ethanol for two hours, diluting the solution with water and acidifying to precipitate the product.

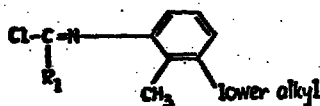
The N-benzoyl-2-cyano-2',3'-dimethyldiphenylamine used as a starting material can be prepared as follows:

119 g. of o-cyanophenol is added to a suspension of 5 g. of 50% sodium hydride in 25 ml. of diethylene glycol dimethyl ether with cooling. After the evolution of hydrogen has ceased, 24.3 g. of N-(2,3-dimethylphenyl)-benzimidoyl chloride (prepared by the action of phosphorus pentachloride on N-benzoyl-2,3-dimethyl aniline in benzene at reflux temperature) is added and the mixture heated at 60°C. for one hour and then briefly at 100°C. The reaction mixture is cooled and diluted with 500 ml. of ether and 100 ml. of petroleum ether. The reaction mixture is washed well with cold water, the organic layer dried, and the solvents evaporated to obtain the desired o - cyanophenyl - N - (2,3 - dimethylphenyl)-benzimidate. The o-cyanophenyl-N-(2,3-dimethylphenyl)benzimidate is heated at 270°C. for 40 minutes to obtain the desired N - benzoyl - 2 - cyano - 2',3' - dimethyldiphenylamine. This product can be purified, if desired, by recrystallization from ethanol-cyclohexane.

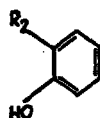
The N-acylated diphenylamine compounds used as starting materials in the practice of the invention can be prepared in a number of ways. For example, an anilide of formula



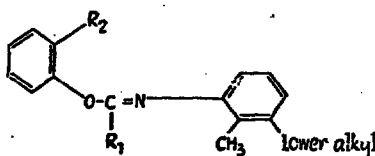
can be reacted with phosphorus pentachloride to produce a benzimidoyl chloride of formula



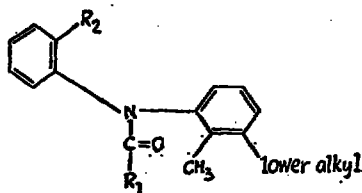
and the benzimidoyl chloride reacted with a phenol compound of formula



or an alkali metal salt thereof and the resulting imido-ester of formula

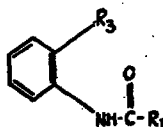


subjected to intramolecular rearrangement by heating to obtain an N-acylated diphenylamine compound of formula

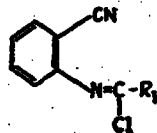


where R₁ is a tertiary alkyl group, such as a tertiary butyl group, or an aryl radical, preferably a phenyl radical which may optionally contain one or more substituents such as halogen, nitro, lower alkyl, lower alkoxy, carboxy and carboalkoxy groups; and R₂ is a cyano, carboxy, carboalkoxy, carboaryloxy, carboarylalkoxy or carboxamide group.

Some of the N-acylated diphenylamine compounds can also be prepared by reacting an N-acylated aniline compound of formula

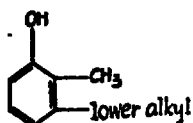


with thionyl chloride, optionally in an organic amine solvent, to obtain the corresponding imino chloride of formula

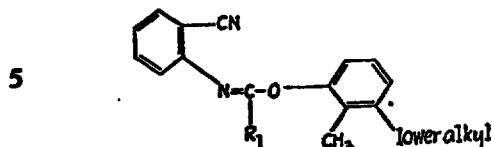


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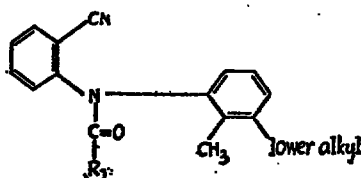
reacting the imino chloride with an alkali metal salt of a phenol of formula



to produce an imidoester of formula



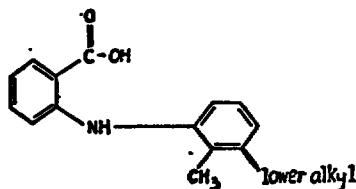
and rearranging the imidoester by heating thereby obtaining an N-acylated diphenylamine of formula



- 10 where R₁ is a cyano or carboxamide group and R₂ has the same significance as given above.

- 15 When it is desired to use an N-acylated-N-(2-methyl-3-alkylphenyl)-anthranilic acid halide as a starting material one can obtain the starting material by treating the corresponding N-acylated N-(2-methyl-3-alkylphenyl)-anthranilic acid compound with a halogenating agent such as thionyl chloride.

- 20 **WHAT WE CLAIM IS:—**
1. New anthranilic acids having the formula



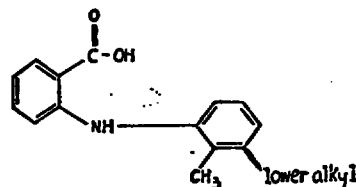
and salts thereof.

- 25 2. N-(2,3-dimethylphenyl)anthranilic acid.
3. N-(2-methyl-3-ethylphenyl)-anthranilic acid.
4. N-(2,3-dimethylphenyl)anthranilic acid sodium salt.
30 5. N-(2,3-dimethylphenyl)anthranilic acid choline salt.

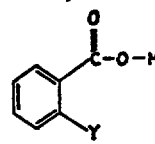
6. N-(2-methyl-3-ethylphenyl)-anthranilic acid choline salt.

7. Process for the production of new anthranilic acids having the formula

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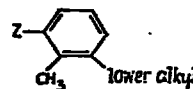


and salts thereof characterized in that a benzoic acid derivative of formula



is condensed with a compound of formula

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and, if desired, the condensation product is thereafter converted either to the free acid or to a salt, where Y and Z are different and represent —NH₂ and halogen; and M is hydrogen or a metal.

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8. Process according to Claim 7 wherein the condensation is carried out in the presence of a copper-containing catalyst and a proton acceptor and the anthranilic acid compound so obtained is thereafter converted by acidification to the free acid.

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9. Process according to Claim 7 or 8 wherein lower alkyl is a methyl group.

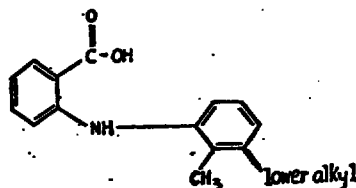
10. Process for producing N-(2,3-dimethylphenyl) anthranilic acid characterized in that an o-halobenzoic acid or a metal salt thereof is condensed with 2,3-dimethyl-aniline in the presence of a copper containing catalyst and a proton acceptor and the N-(2,3-dimethylphenyl)-anthranilic acid compound so produced converted by acidification to the free acid.

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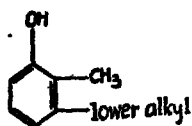
11. Process for the production of new anthranilic acids having the formula

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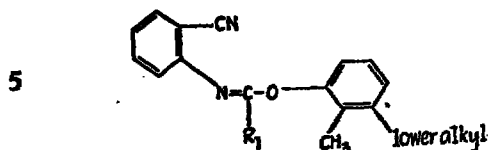




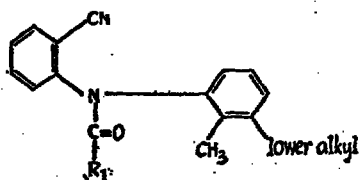
6 reacting the imino chloride with an alkali metal salt of a phenol of formula



to produce an imidoester of formula



and rearranging the imidoester by heating thereby obtaining an N-acylated diphenylamine of formula

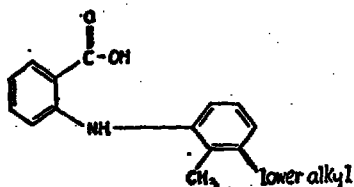


- 10 where R_2 is a cyano or carboxamide group and R_1 has the same significance as given above.

- 15 When it is desired to use an N-acylated-N-(2-methyl-3-alkylphenyl)-anthranilic acid halide as a starting material one can obtain the starting material by treating the corresponding N-acylated N-(2-methyl-3-alkylphenyl)-anthranilic acid compound with a halogenating agent such as thionyl chloride.

WHAT WE CLAIM IS:—

1. New anthranilic acids having the formula



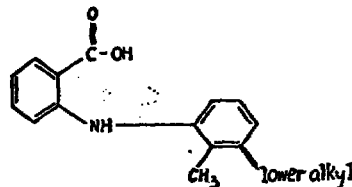
and salts thereof.

- 25 2. N-(2,3-dimethylphenyl)anthranilic acid.
3. N-(2-methyl-3-ethylphenyl)-anthranilic acid.
4. N-(2,3-dimethylphenyl)anthranilic acid sodium salt.
30 5. N-(2,3-dimethylphenyl)anthranilic acid choline salt.

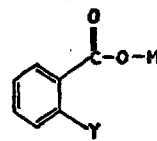
6. N-(2-methyl-3-ethylphenyl)-anthranilic acid choline salt.

7. Process for the production of new anthranilic acids having the formula

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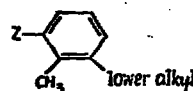


and salts thereof characterized in that a benzoic acid derivative of formula



is condensed with a compound of formula

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and, if desired, the condensation product is thereafter converted either to the free acid or to a salt, where Y and Z are different and represent $-NH_2$ and halogen; and M is hydrogen or a metal.

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8. Process according to Claim 7 wherein the condensation is carried out in the presence of a copper-containing catalyst and a proton acceptor and the anthranilic acid compound so obtained is thereafter converted by acidification to the free acid.

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9. Process according to Claim 7 or 8 wherein lower alkyl is a methyl group.

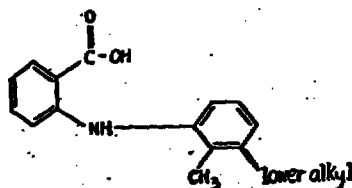
10. Process for producing N-(2,3-dimethylphenyl)anthranilic acid characterized in that an o-halobenzoic acid or a metal salt thereof is condensed with 2,3-dimethyl-aniline in the presence of a copper containing catalyst and a proton acceptor and the N-(2,3-dimethylphenyl)-anthranilic acid compound so produced converted by acidification to the free acid.

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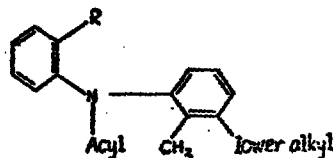
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11. Process for the production of new anthranilic acids having the formula

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and salts thereof characterized in that an acylated diphenylamine compound of formula



- 5 is hydrolyzed, and, if desired, the hydrolysis product is thereafter converted either to the free acid or to a salt; where Acyl represents an acyl radical and R is a carboxy group or a group hydrolyzable to a carboxy group.
- 10 12. Process according to Claim 11 wherein the hydrolysis is carried out under alkaline conditions and the salt of the anthranilic acid so obtained is thereafter converted by acidification to the free acid.

13. Process according to Claim 11 or 12 wherein Acyl is a benzoyl radical which optionally may contain substituents.

14. Process according to Claim 11, 12 or 13, wherein lower alkyl is a methyl group.

15. A process for producing an anthranilic acid having the formula defined in Claim 1 and salts thereof, substantially as described in any one of the foregoing Examples.

16. A pharmaceutical composition containing a compound as claimed in any one of Claims 1 to 6 in association with one or more solid or liquid carriers or diluents.

17. A composition according to Claim 16, made up in a dosage unit form suitable for oral or parenteral administration.

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