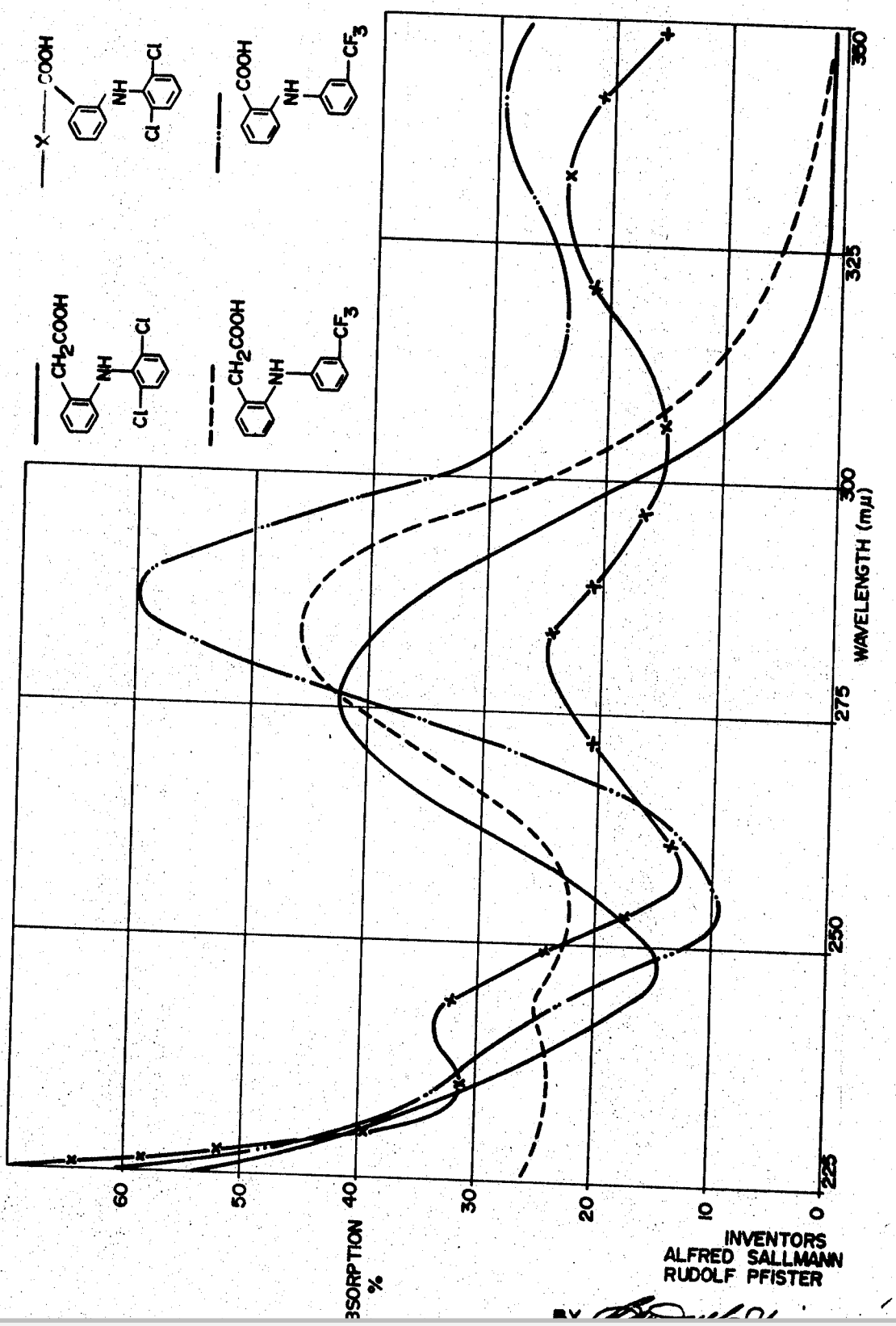
Jan. 26, 1971 A. SALLMANN ET AL 3,558,690

SUBSTITUTED DERIVATIVES OF 2-ANILINOPHENYLACETIC ACIDS AND A PROCESS OF PREPARATION

Filed Sept. 29, 1969



United States Patent Office

3,558,690

Patented Jan. 26, 1971

3,558,690

SUBSTITUTED DERIVATIVES OF 2-ANILINO-PHENYLACETIC ACIDS AND A PROCESS OF PREPARATION

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Continuation-in-part of applications Ser. No. 782,206, and Ser. No. 782,473, both Dec. 9, 1968, and Ser. No. 625,326, Mar. 23, 1967. Said Ser. No. 782,206, being a continuation-in-part of said application Ser. No. 625,326, and Ser. No. 539,829, Apr. 4, 1966. This application Sept. 29, 1969, Ser. No. 861,571

Claims priority, application Switzerland, Apr. 8, 1965, 4,961/65; Feb. 25, 1966, 2,770/66; Mar. 30, 1966, 4,626/66; Dec. 20, 1967, 17,891/67, 17,892/67, 17,893/67

Int. Cl. C07c *101/44*

U.S. Cl. 260—471 27 Claims

ABSTRACT OF THE DISCLOSURE

Substituted 2-anilinophenylacetic acids, their esters and salts have desirable absorption patterns for protecting the skin against the irritating effect of ultraviolet light. The compounds are also antiinflammatory agents. Typical embodiments are 2 - (2,6 - dichloroanilino)-phenylacetic acid, the sodium salt thereof and the methyl ester thereof.

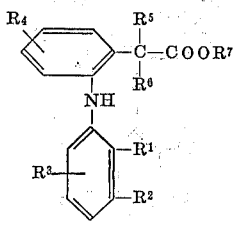
CROSS REFERENCE

This is a continuation-in-part of copending applications Serial Nos. 782,206, 782,473 and 625,326 filed Dec. 9, 1968, Dec. 9, 1968 and Mar. 23, 1967 respectively, Ser. No. 782,206 itself being a continuation-in-part of said Ser. No. 625,326 and of Ser. No. 539,829, filed Apr. 4, 1966 and now abandoned. All of the above listed applications are now abandoned.

DETAILED DESCRIPTION

The present invention pertains to substituted 2-anilinophenylacetic acids, to salts and esters thereof, to methods of treating inflammatory conditions and of protecting skin against irritating ultraviolet light, to compositions adapted for these methods, and to novel synthetic methods for the preparation of these compounds.

In a first embodiment, the present invention pertains to 2-(2-substituted anilino)phenylacetic acids and -acetates of the formula:



I(A)

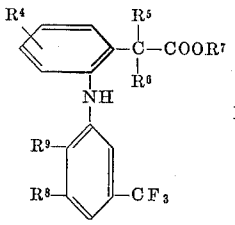
wherein:

R^1 is (lower)alkyl, (lower)alkoxy, fluoro or chloro;
each of R^2 and R^3 is hydrogen, (lower)alkyl, chloro or fluoro;
R^4 is hydrogen, (lower)alkyl, (lower)alkoxy, chloro, fluoro or bromo;
R^5 is hydrogen or (lower)alkyl;
R is hydrogen, (lower)alkyl or when R^5 is hydrogen, benzyl; and
R^7 is hydrogen, (lower)alkyl or benzyl.

The 2-(substituted anilino)phenylacetic acids and -acetates of this first embodiment will necessarily have a sub-

ent, designated by R^1, is a (lower)alkyl, (lower)alkoxy, chloro or fluoro group, preferably methyl or chloro.

In a second embodiment, the present invention pertains to 2-(3-trifluoromethylanilino)phenylacetic acids and -acetates of the formula:



I(B)

wherein:

each of R^4, R^5, R^6 and R^7 is as defined above for Formula I(A);
R^8 is hydrogen or trifluoromethyl; and
R is hydrogen or chloro.

In the compounds of Formula I(A) and (B) and in the present specification, the term (lower)alkyl means a straight or branched monovalent hydrocarbon chain of from 1 to 5 carbon atoms. The term (lower)alkoxy is defined as a (lower)alkyl connected through an ether oxygen link. Thus alkyl includes for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec. butyl, and tert. butyl, preferably methyl or ethyl, while (lower)alkoxy includes for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, and isobutoxy, perferably methyl or ethyl.

The compounds of Formulas I(A) and I(B) absorb the irritating rays of ultraviolet light which are primarily responsible for sunburn, those of a wavelength of about 290 to about 300–315 millimicrons, while at the same time they do not absorb the desirable so-called "tanning" rays of over 315 millimicrons wavelength. These compounds are, therefore, especially useful as ultraviolet absorbers for cosmetic purposes, e.g., in sun-tan creams or lotions. The corresponding anthranilic acid derivatives, on the contrary, show a distinct and pronounced absorption of the desired "tanning" radiation. The diagram shown in the accompanying drawing illustrates the absorption of ultraviolet light of wavelengths in the "sunburn-causing" and "tanning" ranges of two preferred compounds according to the invention, on the one hand, and to structurally similar anthranilic acid derivatives, on the other hand.

The compounds advantageously also possess antiinflammatory, analgesic and antipyretic activity combined with a favorable therapeutic index. This activity can be observed in various standard pharmacological tests, as for example in the bolus alba test in rats, the UV-erythema test in guinear pigs, the cotton pellet test in rats, the phenylquinone stretch test in mice, etc. These properties render the compounds of the invention additionally suitable for the treatment of rheumatic, arthritic and other inflammatory conditions.

As an example of the anti-inflammatory activity of the compounds, the sodium salt of 2-(2,6-dichloroanilino)-phenylacetic acid demonstrates a significant inhibitory effect in bolus alba induced edema in the rat paw, described by G. Wilhelmi, Jap. Journ. Pharmac. 15, 190 (1965).

Topical sun-tan compositions according to the invention contain at least one compound of Formulas I(A) or I(B) or a pharmaceutically acceptable salt thereof with a base, in an amount which absorbs a sufficient amount of ultraviolet radiation having a wavelength in the range of from 290 to 315 millimicrons, as well as a carrier compatible with the compound or salt, the carrier being of a creamy to highly fluid consistency

When utilized primarily for their anti-inflammatory activity, the compounds of the present invention can also be administered orally, rectally or parenterally, in particular intramuscularly. The 2-(substituted anilino)phenylacetate esters falling under Formulas I(A) and I(B) are principally administered orally or rectally. Suitable pharmaceutical forms include solid and liquid unit oral dosage forms such as tablets, capsules, powders, suspensions, solutions, syrups and the like, including sustained release preparations, and fluid injectable forms such as sterile solutions and suspensions. The term dosage form as used in this specification and the claims refer to physically discrete units to be administered in single or multiple dosage to animals, each unit containing a predetermined quantity of active material in association with the required diluent, carrier or vehicle. The quantity of active material is that calculated to produce the desired therapeutic effect upon administration of one or more of such units.

Powders are prepared by comminuting the compound to a suitably fine size and mixing with a similarly comminuted diluent pharmaceutical carrier such as an edible carbohydrate material as for example, starch. Sweetening, flavoring, preservative, dispersing and coloring agents can also be present.

Capsules are made by preparing a powder mixture as described above and filling formed gelatin sheaths. A lubricant such as talc, magnesium stearate and calcium stearate can be added to the powder mixture as an adjuvant before the filling operation; a glidant such as colloidal silica may be added to improve flow properties; a disintegrating or solubilizing agent may be added to improve the availability of the medicament when the capsule is ingested.

Tablets are made by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base such as starch, sucrose, kaolin, dicalcium phosphate and the like. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acacia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the resulting imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The medicaments can also be combined with free flowing inert carriers and compressed into tablets directly without going through the granulating or slugging steps. A protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as syrups and elixirs can be prepared in unit dosage form so that a given quantity, e.g., a teaspoonful, contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous sucrose solution while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the medicament in a non-toxic vehicle in which it is insoluble.

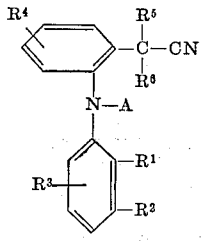
For parenteral administration, fluid unit dosage forms can be prepared by suspending or dissolving a measured amount of the compound in a non-toxic liquid vehicle suitable for injection such as an aqueous or oleaginous medium. Alternatively a measured amount of the compound is placed in a vial and the vial and its contents are sterilized and sealed. An accompanying vial or vehicle can be provided for mixing prior to administration

pounds of Formulas I(A) or I(B) or pharmaceutically acceptable salts thereof with a base, for the treatment of rheumatic, arthritic and other inflammatory conditions is from about 50 to about 1500 mg. for adult patients, although the amounts administered depend upon the species, age and weight of the subject under treatment, as well as the particular condition to be treated and the mode of administration. Dosage units such as dragees, tablets or suppositories, preferably contain from about 25 to about 300 mg. of a compound of Formulas I(A) or I(B) or a pharmaceutically acceptable salt thereof. Unit dosages for oral administration preferably contain from 1% to 90% of an active ingredient of Formula I(A) or I(B).

Pharmaceutically acceptable salts of the acids falling under Formulas I(A) or I(B) are obtained either in the courses of the production of the acids as described hereafter, or via conventional methods, such as the mixing of preferably equimolar amounts of the free acid and the base in a suitable solvent, such as water, methanol, ethanol, diethyl ether, chloroform, methylene chloride or the like. Salts, which in certain solvents have an appreciably lower solubility than the alkali salts, can also be produced from the latter by double reaction. Pharmaceutically acceptable salts of the acids falling under Formulas I(A) and I(B) are such as derived from non-toxic inorganic or organic bases. Examples of such salts are the sodium, potassium, lithium, magnesium, calcium and ammonium salts, as well as salts with ethylamine, triethylamine, 2-aminoethanol, 2,2-iminodiethanol, 2-dimethylamino-ethanol, 2-diethylamino-ethanol, ethylenediamine, benzylamine, p-aminobenzoic acid, 2-diethylaminoethyl ester, pyrrolidine, piperidine, morpholine, 1-ethylpiperidine or 2-piperidino-ethanol, and the like. A particular advantage of the salts is that they tend to stabilize the acids falling under Formulas I(A) and I(B).

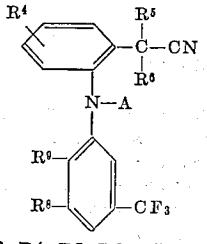
The compounds of the present invention can be prepared in a number of ways.

In a first process, a 2-(substituted anilino)phenylacetonitrile of the formula:



II(A)

or of the formula:



II(B)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are as defined above and A is hydrogen or a (lower)alkanoyl group, is treated with an alkali metal hydroxide in an aqueous solvent. Suitable solvents include aqueous lower alkanols such as ethanol, methanol or n-butanol, polyols such as ethylene glycol or dimethylformamide. The hydrolysis is performed at or slightly below the boiling temperature of the solvent, using at least two equivalents of an alkali metal hydroxide, in particular sodium or potassium hydroxide.

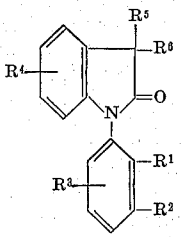
The 2-(substituted anilino)phenylacetonitriles of Formulas II(A) and II(B) where A is (lower)alkanoyl can

trile with a (lower)alkanol in the presence of an acid catalyst. (Lower)alkyl and benzyl 2-(substituted anilino) phenylacetates can also be obtained from the corresponding free acids through standard esterification techniques. Conversely the (lower)alkyl 2 - (substituted anilino) phenylacetates can be saponified and the benzyl 2-(substituted anilino)phenylacetates hydrogenolysized with catalytically activated hydrogen to yield in both cases the corresponding 2-(substituted anilino)phenylacetic acids.

The starting materials of Formulas II(A) and II(B) are obtained from the corresponding 2-(substituted anilino)anthranilic acids or their (lower)alkyl esters through reduction with lithium aluminum hydride in ether or tetrahydrofuran, sodium borohydride in methanol, or sodium borohydride and lithium bromide in diglyme (diethylene glycol dimethyl ether). The resultant 2-(substituted anilino)benzylalcohols are then converted to the corresponding benzyl chlorides through treatment with acetyl chloride, with dry ethereal hydrogen chloride, or with thionyl chloride and dry pyridine in ether. These 2-(substituted anilino)benzyl chlorides are then treated with sodium or potassium cyanide to yield the requisite 2-(substituted anilino)phenylacetonitriles of Formulas II(A) or II(B).

The groups R^5 or R^6 can be introduced into a 2-(substituted anilino)phenylacetonitrile of Formula II(A) or II(B) wherein A is a (lower)alkanoyl group and R^5 and R^6 are hydrogen or into the corresponding 2-(substituted anilino)phenylacetic acid bearing an N-alkanoyl group, through conventional alkylation techniques, with the N-alkanoyl group subsequently being removed by alkaline hydrolysis.

In a second process an indolinone of the formula:



III(A)

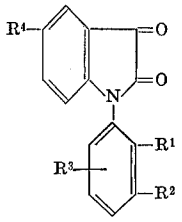
is treated with at least one equivalent of an alkali metal hydroxide, alkali metal carbonate or alkaline earth metal hydroxide with heating and, if desired, the acid is liberated from the alkali or alkaline earth salt thus obtained. This acid can be converted into another salt with an organic or inorganic base if desired. Suitable solvents for this second process are, in particular, aqueous lower alkanols such as ethanol, methanol or n-butanol; ethylene glycol; or dimethylformamide. The hydrolysis is performed at or slightly under the boiling point of the solvent.

The indolinones of Formula III(A) are obtained from substituted N-phenylanilines (obtained for example from optionally substituted o-chloro- or o-bromo- benzoic acids and substituted anilines followed by decarboxylation of the o-anilino-benzoic acids formed, or by heating N,O-diaryl-iminoesters and hydrolysing the N,N-diarylamides formed by rearrangement, or by reacting an optionally substituted acetanilide with a bromobenzene substituted by a group corresponding to R^4) through the reaction of the substituted N-phenyl aniline with an α-chloroalkanoic acid chloride, e.g., chloroacetyl chloride, 2-chloropropionyl chloride and the like, to yield an N-(α-chloroalkanoyl) (N-substituted phenyl)aniline. This is then heated with aluminum chloride as a melt at temperatures of about 160° C.

The substituents R^5 and R^6 can also be directly introduced into an indolinone of Formula III(A). Thus an indolinone of formula III(A) wherein R^5 and R^6 are hydrogen is treated with an alkyl halide or dialkyl sulfate in the presence of sodium hydride or sodium amide in dimethylformamide, or with an aralkyl halide, such as ben-

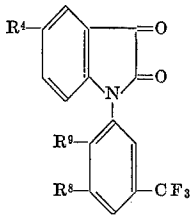
and then reducing the 1-aryl-3-benzal-2-indolinone formed; e.g., with activated hydrogen.

In a third process an N-substituted indol-2,3-dione of the formula:



IV(A)

or of the formula:

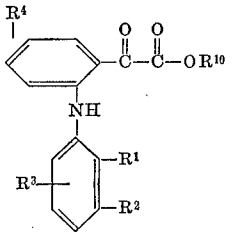


IV(B)

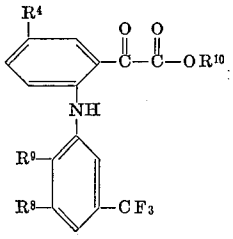
wherein R^1, R^2, R^3, R^4, R^8 and R^9 are as previously defined, is treated first with hydrazine or a semicarbazide and then with an alkali hydroxide or alkali metal alcoholate. This process is carried out by either first converting the substituted indole-2,3-dione with hydrazine, which can also be used in the form of the hydrate, or with semicarbazide to the corresponding 3-(hydrazone) or 3-(semicarbazone), respectively, and decomposing this intermediate with an alkali metal hydroxide or alkali metal alkoxides or by mixing and reacting all three reaction components simultaneously. The temperature for the main reaction, the action of the alkali metal hydroxide or alkali metal alkoxide, is in the range of 100–220°, preferably from 140–200°. The optional prior and separate formation of the hydrazone can be carried out at considerably lower temperatures, e.g., at room temperature; it can however also be conducted at higher temperatures. Water which may be introduced when the hydrazine hydrate is used or that which is liberated by the reaction, can be removed by distillation. A higher boiling organic solvent can be used as reaction medium. Such solvents include ethylene glycol (or mono- and di- ethers thereof such as diethylene glycol, diethylene glycol monomethylether) or triethylene glycol, higher boiling alcohols such as benzyl alcohol, octyl alcohol or nitrilotriethanol, or when the reaction is carried out in a closed vessel, a (lower)alkanol. It is also possible when employing a (lower)alkanol solvent such as ethanol or butanol as the initial reaction medium, to remove this solvent during the reaction together with excess hydrazine and liberated water until the reaction mixture gradually solidifies, reaching a temperature between 150° and 200°. The alkali metal hydroxides which can be used in this third process are, in particular, potassium or sodium hydroxide. The alkali metal alkoxides include sodium alkoxide and are either derivatives of (lower)alkanol solvent or of the higher boiling hydroxy compounds used as reaction media.

The alkali metal salts of substituted phenylacetic acids of Formula I(A) or I(B) that are first obtained according to this process are optionally converted into the free acid in the usual manner using strong acids, e.g., hydrochloric acid. If desired, the acid obtained is converted into another salt, preferably a pharmaceutically acceptable salt, with an inorganic or organic base, according to processes mentioned hereinbefore.

In converting the ring-substituted indol-2,3-diones of Formula IV(A) or IV(B) into the corresponding phenylacetic acids, the process can be carried out through an additional intermediate stage, namely the production of



V(A)

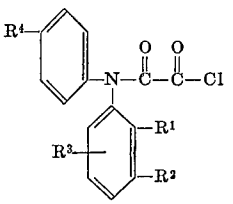


V(B)

wherein R^1, R^2, R^3, R^4, R^8 and R^9 are as previously defined and R^{10} is hydrogen or a cation.

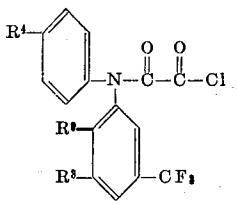
Thus a compound of Formula IV(A) or IV(B) is initially subjected to hydrolysis and 2-(substituted anilino) phenylglyoxylic acid or its salt is then reduced with hydrazine or semicarbazide and with an alkali metal hydroxide or alkali metal alkoxide as previously described.

The third method is especially advantageous both in terms of its yield and of its application. Thus in the second method described above, the relatively high temperatures utilized in the aluminum chloride ring closure can lead to a number of undesirable side reactions, including loss or exchange of fluoro in trifluoromethyl groups, migration of alkyl groups and splitting of alkoxy groups. Such are avoided in the preparation of the indol-2,3-diones of Formulas IV(A) and IV(B) as can be seen in the following description of these starting materials. Thus a substituted N-phenylaniline, obtained for example as previously described, is treated with oxalyl chloride to yield a substituted N-phenyl oxanilic acid of the formula:



VI(A)

or of the formula



VI(B)

wherein R^1, R^2, R^3, R^4, R^8 and R^9 are as previously defined.

These oxanilic acid chlorides can then be converted into the corresponding indol-2,3-diones of Formulas IV(A) and IV(B) respectively, through the use of aluminum chloride, the reaction being conducted however at room temperature.

Yields are further improved if the indol-2,3-dione is purified, as through recrystallization, prior to treatment with hydrazine or a semicarbazide.

As previously described, the 2-(substituted anilino)-

use of conventional techniques. These includes the use of a lower diazoalkane, such as diazomethane, in an inert organic solvent such as ether, methylene chloride, benzene, acetals of N,N-dimethylformamide, i.e., 1,1-diethoxytrimethylamines or 1,1-diaralkoxytrimethylamines, etc.; the use of benzyl alcohol or (lower)alkanols in the presence of N,N-dimethyl formaldehyde dineopentyl acetal, i.e., 1,1-dineopentyloxytrimethylamine; the raction of an alkali salt of an acid falling under Formulas I(A) or I(B) and a reactive ester of a (lower)alkanol or benzyl alcohol, e.g., with dimethylsulfate, diethylsulfate, methyl iodide, ethyl iodide, propyl bromide, butyl bromide, benzyl chloride, benzyl bromide or p-toluenesulfonic acid methyl ester in a suitable reaction medium; and the reaction of an acid falling under Formulas I(A) or I(B) with a mixture consisting of the alcohol desired as ester component and thionyl chloride. In this last method, the maintenance of low temperatures, e.g., below about −5°, is advantageous.

The following examples set forth the manner and process of making typical embodiments of the invention, without being a limitation thereof, and include the best mode contemplated by the inventors for carrying out the invention. In these examples, temperatures are expressed on the centigrade scale.

EXAMPLE 1

2-(2,6-dichloro-3-methylanilino)phenylacetic acid

(A) N-phenyl-2,6-dichloro - 3 - methylaniline: Seven grams of 2-(2,6-dichloro-3-methylanilino)benzoic acid [alternatively named as N-(2,6-dichloro-m-tolyl)-anthranilic acid] are heated for 2 hours at 280°. The cooled melt is dissolved in 30 ml. of benzene and the bnzene solution is extracted with 5 ml. of 2 N sodium carbonate and 5 ml. of water. The solution is dried with sodium sulfate and concentrated. The residue is distilled whereupon N-phenyl-2,6-dichloro-3-methylaniline (alternatively named as 2,6-dichloro-N-phenyl-m-toluidine) is obtained as a yellow oil, B.P. 115–120°/0.001 torr.

The following are obtained in a similar fashion from the corresponding anthranilic acids:

(a) N-phenyl-2,6-dichloroaniline, B.P. 109–111°/0.003 torr.

(b) N-phenyl-2-chloro-6-methylaniline, B.P. 88°/0.005 torr.

Alternatively, these substituted N-phenylanilines can be prepared according to the following procedures:

Forty milliliters of acetyl chloride are slowly added dropwise to a solution of 81 g. of 2,6-dichloraniline in 30 ml. of glacial acetic acid. The solution is then heated in a water bath until the development of hydrogen chloride has been completed. It is then cooled to room temperature and the mixture is poured into ice. The crystals which separate are filtered off and recrystallised from glacial acetic acid to yield N-acetyl-2,6-dichloraniline, M.P. 180–181°. The yield is 70% of the theoretical.

N-acetyl-2,6-dichloro-3-methylaniline M.P. 179–181° from glacial acetic acid/water, is prepared analogously.

Fifteen grams of N-acetyl-2,6-dichloroaniline (alternatively named as 2,6-dichlor-acetanilide) are dissolved in 150 ml. of bromobenzene. Five and a half grams of calcinated potassium carbonate and 0.5 g. of copper powder are added. The mixture is refluxed for 4 days, the water formed being removed by a water separator, cooled and subjected to steam distillation. The residue is extracted with 200 ml. of ether. The ether solution is filtered through Hyflo and the residue is concentrated to dryness under 11 torr. The residue is dissolved in 60 ml. of 10% ethanolic potassium hydroxide solution and the solution is refluxed for 3 hours. The solution is then concentrated to dryness at 40° under 11 torr. Ten milliliters of water are added to the residue which is then extracted with 100 ml. of ether. The ether solution is removed and extracted with 20 ml. of

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