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OXINDOLE CARBOXAMIDES

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ABSTRACT OF THE DISCLOSURE

A series of novel 2-oxo-2,3-dihydroindole-3-carboxamides have been prepared, including their pharmaceutically acceptable salts. These compounds are useful in therapy as non-steroidal anti-inflammatory agents, with 2',4'-difluoro - 1 - ethyl - 2 - oxo - -5 - bromo - 2,3 - dihydroindole-3-carboxanilide and 1-ethyl-2-oxo-5,6-dichloro-2,3-dihydroindole-3-carboxanilide being the key compounds of choice. Alternate methods of preparation are provided and some of these synthetic routes are described in detail.

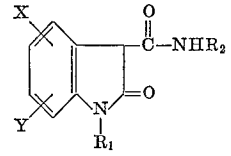
BACKGROUND OF THE INVENTION

This invention relates to new and useful oxindole carboxamides, and to their various novel methods of preparation. More particularly, it is concerned with a novel series of 2-oxo-2,3-dihydroindole-3-carboxamides, which are of especial value in view of their chemotherapeutic properties.

In the past, various attempts have been made by numerous investigators in the field of organic medicinal chemistry to obtain new and useful anti-inflammatory agents. For the most part, these efforts have involved the synthesis and testing of various steroidal hormone compounds such as the corticosteroids. However, in the search for still newer and better anti-inflammatory agents, far less is known about the effect of non-steroidal agents in this area, albeit this would be attractive since they would also necessarily lack the untoward steroidal side-effects.

SUMMARY OF THE INVENTION

In accordance with the present invention, it has now been found that various novel oxindole carboxamide compounds, i.e., non-steroids, are surprisingly, extremely useful when employed in the field of the drug therapy as anti-inflammatory agents. More specifically, the novel compounds of this invention are 2-oxo-2,3-dihydroindole-3-carboxamides of the formula:



and the base salts thereof with pharmacologically acceptable cations, wherein X and Y are each a member selected from the group consisting of hydrogen, fluorine, chlorine, bromine, alkyl and alkoxy each having from one to five carbon atoms, trifluoromethyl and trifluoromethoxy; R_1 is a member selected from the group consisting of hydrogen, 2,2,2-trifluoroethyl, alkyl having from one to six carbon atoms, alkenyl having up to four carbon atoms and phenylalkyl having up to three carbon atoms in the alkyl moiety; and R_2 is a member selected from the group consisting of naphthyl, phenyl, and mono- and di-substituted phenyl wherein each substituent is chosen from the group consisting of fluorine, chlorine and bromine, alkyl having up to four carbon atoms, alkoxy and thioalkoxy each having up to three carbon atoms, trifluoromethyl and trifluoromethoxy. These novel compounds are all

useful in alleviating the painful effects caused by various inflammatory conditions.

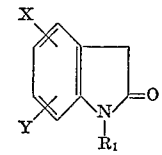
Of especial interest in this connection are such typical member compounds of the invention as

4'-chloro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide,
4'-chloro-1-(n-propyl)-2-oxo-2,3-dihydroindole-3-carboxanilide,
3',4'-dichloro-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide,
3'-fluoro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide,
4'-fluoro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide,
2',4'-difluoro-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide,
2',4'-difluoro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide,
2',5'-difluoro-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide,
2',5'-difluoro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide,
2',5'-difluoro-1-(n-propyl)-2-oxo-2,3-dihydroindole-3-carboxanilide,
2',4'-difluoro-1-ethyl-2-oxo-5-chloro-2,3-dihydroindole-3-carboxanilide,
2',4'-difluoro-1-ethyl-2-oxo-5-bromo-2,3-dihydroindole-3-carboxanilide,
1-ethyl-2-oxo-5,6-dichloro-2,3-dihydroindole-3-carboxanilide, and
4'-fluoro-1-ethyl-2-oxo-5,6-dichloro-2,3-dihydroindole-3-carboxanilide.

It is also to be understood that many of these compounds are tautomeric and exist in the enolic form with respect to the 2-position of the molecule. All these compounds are extremely potent and possess anti-inflammatory activity to a significantly high degree.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the process employed for preparing the novel compounds of this invention, an appropriately substituted 2-oxo-2,3-dihydroindole compound of the formula:



is contacted with an organic isocyanate reagent of the formula R_2NCO wherein R_2 corresponds to the previously defined organic nitrogen substituent on the carboxamide moiety of the desired final product. In this way, the corresponding 3-carboxamide (—$CONHR_2$) compound is formed where X, Y and R_1 are all defined as previously indicated. This particular reaction is normally conducted in a basic solvent medium, most desirably employing a reaction-inert organic solvent such as tetrahydrofuran, dimethylsulfoxide or dimethylformamide and preferably using a slight excess in moles of a base, like triethylamine, which may be admixed with the solvent. Many of the aforesaid isocyanates (R_2NCO) are either known compounds or else they can easily be prepared, using methods well-known to those skilled in the art, starting from readily available materials. In practice, it is usually preferable to employ at least about a molar equivalent of the isocyanate reagent in the instant reaction of the present invention, with best results often being achieved by using just a slight excess of same. Although any temperature below that of reflux may be used in order to effect the reaction, it is normally found most convenient to employ

elevated temperatures in almost every case so as to shorten the required reaction time, which may range anywhere from several minutes up to about 24 hours depending, of course, upon the particular carboxamide compound actually being prepared. Upon completion of the reaction, the product is easily recovered from the spent reaction mixture by pouring same into an excess of ice-water containing a slight excess of acid, such as hydrochloric acid, whereby the carboxamide compound readily precipitates from solution and is subsequently collected by such means as suction filtration and the like.

Alternatively, the 2-oxo-2,3-dihydroindole - 3 - carboxamide compounds of this invention may also be prepared by treating the corresponding 3- or 4-carboxylic acid esters with at least an equimolar amount of an amine of the formula R_2NH_2, wherein R_2 is as previously defined. More specifically, this particular process of the invention involves reacting a carbalkoxy ester of the aforesaid type with an appropriate amine base in a reaction-inert organic solvent medium, whereby the desired aminolysis reaction takes place. The reaction is generally conducted by mixing the two components together in said solvent system at or near room temperature, and then refluxing the resultant system for a period of about one-half to four hours. Although it is only necessary that these two reactants be present in substantially equimolar amounts in order to effect the reaction, a slight excess of one or the other (and preferably the more readily available amine base reagent) is not harmful in this respect and may even serve to shift the aminolysis reaction to completion. Preferred reaction-inert organic solvents for use in the aminolysis reaction include such lower N,N-dialkyl alkanolamides as dimethylformamide, dimethylacetamide and the like, as well as such aromatic hydrocarbon solvents as benzene, toluene, xylene and so forth. In some instances where a lower alkyl ester is employed as starting material and the two reactants are mutually miscible, it may even be desirable or at least possible to conduct the reaction in the absence of a solvent. In any event, it may be found most helpful and usually suitable to distill off the volatile alcohol by-product as soon as it is formed in the reaction and thereby shift the aminolysis equilibrium to completion in this manner. Included among the many typical 2-oxo-2,3-dihydroindole-3-carboxylate esters of this invention which may be used as substrates in the aminolysis reaction are the methyl, ethyl, n-propyl, isopropyl, n-butyl and isoamyl esters. Upon completion of the reaction, the desired carboxamide final product is generally most conveniently isolated from the mixture by distilling off the alcohol by-product, as aforesaid, until the temperature of the volatile alcohol solvent vapors in the distilling head approximates in terms of degrees centigrade the temperature of the reaction mixture in the flask (i.e., the distilland). At this point, the resulting distilland is cooled to room temperature and the product subsequently precipitates from solution.

The 2-oxo-2,3-dihydroindole-3-carboxylate esters, used as described above as intermediates to form the corresponding 3-carboxamides of this invention, are themselves prepared by a facile one-step synthesis starting from readily available materials. For instance, in the case of ethyl 1-methyl-2-oxo-2,3-dihydroindole-3-carboxylate and related compounds, such products are normally prepared by simply condensing a known 2-oxo-2,3-dihydroindole starting material, like 1-methyl-2-oxo-2,3-dihydroindole (R. Stollé in German Pat. No. 335,673) or a commercially available 2-oxo-2,3-dihydroindole like the corresponding 1-ethyl derivative, with diethyl carbonate in the presence of an alkali metal alkoxide reagent, such as sodium methoxide, to form the desired corresponding 2-oxo-2,3-dihydroindole-3-carboxylate ester.

A still further method for preparing the instant compounds of this invention involves reacting a 2-oxo-2,3-dihydroindole in the form of an alkali metal or alkaline-earth metal salt with an appropriate 1,1,3-trisubstituted urea of the formula $(R'')_2NCONHR_2$, wherein R''_2 is an aryl group such as phenyl, p-chlorophenyl, p-bromophenyl, p-nitrophenyl, p-acetylaminophenyl, p-tolyl, p-anisyl, α-naphthyl, β-naphthyl, and the like. This reaction is preferably carried out in the presence of a reaction-inert polar organic solvent medium. Typical organic solvents for use in this connection include the N,N-dialkyl lower alkanoamides like dimethylformamide, dimethylacetamide, diethylformamide and diethylacetamide, as well as lower dialkyl sulfoxides such as dimethyl sulfoxide, diethyl sulfoxide and di-n-propyl sulfoxide, etc., in addition to hexamethyl-phosphoramide. It is desirable that the aforesaid solvent for this reaction be present in sufficient amount to dissolve each of the previously mentioned starting materials. In general, the reaction is conducted at a temperature that is in the range of from about 20° C. up to about 150° C. for a period of about one-half to about ten hours. Recovery of the desired product from the reaction mixture is then most conveniently accomplished by first diluting the reaction solution with water and then adjusting the resulting aqueous solution to at least about pH 8.0, followed by subsequent extraction of the basic aqueous solution with any water-immiscible organic solvent in order to remove minor amounts of unreacted or excess starting material that might possibly be present at this stage. Isolation of the desired 2-oxo-2,3-dihydroindole-3-carboxamide from the basic aqueous layer is then effected by the addition thereto of a dilute aqueous acid solution, wherein the acid is present in sufficient amount to cause precipitation of said indolecarboxamide to occur from the aqueous solution.

In connection with a more detailed consideration of the preferred method of synthesis of this invention, the relative amounts of reagents employed are such that the molar ratio of the 2-oxo-2,3-dihydroindole to the 1,1-diaryl-3-(monosubstituted)urea is desirably in the preferred range of from about 1:1 to 1:3, although substantially equimolar ratios will still cause equally satisfactory results to be achieved. Nevertheless, an excess of the trisubstituted urea is normally employed in this reaction since this not only serves to cause a shift in the reaction equilibrium to the product side of the equation, but it is also additionally advantageous in that the excess reagent is easily removed after completion of the reaction by means of the solvent extraction step previously referred to. Moreover, it is to be noted that the formation of the carboxamide final products of this invention is greatly enhanced by the overall basic character of the reaction mixture.

The two major type starting materials required for this reaction, viz, the 2-oxo-2,3-dihydroindoles and the 1,1-diaryl-3-(monosubstituted)ureas, are both readily available to those skilled in the art. For instance, the 2-oxo-2,3-dihydroindoles, which are also used as starting materials in the previously described isocyanate method, as well as in the preparation of the corresponding 3-carboxylic acid ester intermediates, are either available commercially or else they are well-known in the chemical prior art and/or can easily be synthesized in accordance with standard organic procedures that are commonly described therein [e.g., see P. L. Julian et al., in "Heterocyclic Compounds," vol. 3, John Wiley & Sons, Inc., New York (1962), pp. 142–143, for a general description of the Stollé synthesis starting from the corresponding α-haloacetanilides]. The 1,1-diaryl-3-(monosubstituted)ureas, on the other hand, are all readily prepared from common organic reagents by employing standard procedures well known in the art, e.g., the desired 1,1,3-trisubstituted urea may be prepared from the corresponding disubstituted carbamyl chloride $[R''_2)_2NCOCl]$ and the appropriate amine (R_2NH_2) in accordance with the general procedure of Reudel, as described in Recueil des Travaux Chimiques des Pays-Bas, vol. 33, p. 64 (1914).

The chemical bases which are used as reagents in this invention to prepare the pharmaceutically acceptable salts

of same are those which form non-toxic salts with the many herein described acidic 2-oxo-2,3-dihydroindole-3-carboxamides, such as 2',4' - difluoro - 1 - ethyl - 2 - oxo-5-bromo-2,3-dihydroindole-3-carboxanilide, for example. These particular non-toxic base salts are of such a nature that their cations are said to be essentially non-toxic in character over the wide range of dosage administered. Examples of such cations include those of sodium, potassium calcium and magnesium, etc. These salts can easily be prepared by simply treating the aforementioned 2-oxo-2,3-dihydroindole-3-carboxamides with an aqueous solution of the desired pharmacologically acceptable base, i.e., those oxides, hydroxides or carbonates which contain pharmacologically acceptable cations, and then evaporating the resulting solution to dryness while preferably being placed under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the said acidic compounds and the desired alkali metal alkoxide together, and then evaporating said resulting solution in the same manner as before. In either case, stoichiometric amounts of reagents must be employed in order to ensure completeness of reaction, with consequent maximum production of yields of the desired pure product.

As previously indicated, the 2-oxo-2,3-dihydroindole-3-carboxamide compounds of the present invention are all readily adapted to therapeutic use as anti-inflammatory agents, particularly in view of their ability to reduce the swelling and relieve the pain caused by arthritic and other inflammatory disorders that are normally associated with such basic ailments as rheumatoid arthritis and the like. For instance, 2',4'-difluoro-1-ethyl-2-oxo-5-bromo-2,3-dihydroindole - 3 - carboxanilide and 1-ethyl-2-oxo-5,6-dichloro-2,3-dihydroindole-3-carboxanilide, both typical and preferred agents of the present invention, exhibit remarkable activity in the standard carrageenin-induced rat foot edema test [described by C. A. Winter et al., Proc. Soc. Exp. Biol., vol. III, p. 544 (1962)], where it was found that the former compound is almost about one-half as active as indomethacin as regards potency, while the latter carboxamide agent of this invention is just about as active as the former compound in this respect. More specifically, 2',4' - difluoro-1-ethyl-2-oxo-5-bromo-2,3-dihydroindole-3-carboxanilide and 1-ethyl-2-oxo-5,6-dichloro-2,3-dihydroindole-3-carboxanilide have been found to exhibit their effect in rats when tested orally at levels ranging from 0.33–33 mg./kg., with both compounds still retaining their extremely potent anti-inflammatory activity in adrenalectomized animals to a significantly high degree. Additionally, none of these compounds causes substantial side effects to occur in the subject to whom they are so administered, i.e., no problems of toxicity or of a harmful pharmacological nature, either gross or microscopic, are encountered when said compounds are administered for the aforestated purposes in the manner described as indicated above.

In accordance with a method of treatment of the present invention, the herein described 2-oxo-2,3-dihydroindole-3-carboxamide anti-inflammatory agents can be administered to an afflicted subject via either the oral or parenteral routes of administration. In general, these compounds are most desirably administered in doses ranging from about 10 mg. up to about 1000 mg. per day, although variations will still necessarily occur depending upon the weight of the subject being treated. However, a dosage level that is in the range of from about 0.16 mg. to about 16 mg. per kg. of body weight per day is most desirably employed in order to achieve effective results. Nevertheless, it is still to be appreciated that other variations may also occur in this respect, depending upon the species of animal being treated and its individual response to said medicament, as well as on the particular type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful or deleterious side effects to occur provided that such higher dose levels are first divided into several smaller doses that are to be administered throughout the day.

In connection with the use of the 2-oxo-2,3-dihydroindole-3-carboxamide compounds of this invention for the treatment of arthritic subjects, it is to be noted that they may be administered either alone or in combination with pharmaceutically acceptable carriers by either of the routes previously indicated, and that such administration can be carried out in both single and multiple dosages. More particularly, the novel compounds of the invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically-acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, such oral pharmaceutical compositions can be suitably sweetened and/or flavored by means of various agents of the type commonly employed for just such a purpose. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 0.5% to about 90% by weight of the total composition, i.e., in amounts which are sufficient to provide the desired unit dosage.

For purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and dicalcium phosphate may be employed along with various disintegrants such as starch and preferably potato or tapioca starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules; preferred materials in the connection would also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dye, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For purposes of parenteral administration, solutions of these particular 2-oxo-2,3-dihydroindole-3-carboxamides in either sesame or peanut oil or in aqueous propylene glycol may be employed, as well as sterile aqueous solutions of the corresponding water-soluble alkali metal or alkaline-earth metal salts previously enumerated. Such aqueous solutions should be sutiably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular solutions are especially suitable for intravenous, intramuscular and subcutaneous injection purposes. Additionally, it is also possible to administer the aforesaid indolecarboxamide compounds topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, salves, jellies, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

A general procedure employed for detecting and comparing the anti-inflammatory activity of the compounds of the present invention is, as previously indicated, the standard carrageenin-induced rat foot edema test using the aforementioned technique of C. A. Winter et al. In this test, anti-inflammatory activity is determined as the inhibition of edema formation in the hind paw of male albino rats (weighing, 150–190 g.) in response to a subplantar

injection of carrageenin. The carrageenin is injected as a 1% aqueous suspension (0.05 ml.) one hour after oral administration of the drug in the form of an aqueous solution. Edema formation is then assessed three hours after the carrageenin injection by measuring the volume of the injected paw initially as well as at the three-hour mark. The increase in volume three hours after carrageenin injection constitutes the individual response. Compounds are considered active if the response between the drug-treated animals (six rats/group) and the control group (i.e., animals receiving the vehicle alone) is deemed to be significant on comparison with standard compounds like acetylsalicylic acid at 100 mg./kg. or phenylbutazone at 33 mg./kg., both by the oral route of administration.

EXAMPLE I

A slurry of 1.09 g. (0.024 mole) of sodium hydride (a 52.6% dispersion in mineral oil) suspended in 30 ml. of dry dimethylformamide was stirred at room temperature, while 2.94 g. (0.020 mole) of 1-methyl-2-oxo-2,3-dihydroindole, divided into small portions, was subsequently added thereto with continued stirring. At this point, 3.20 g. (0.024 mole) of m-tolyl isocyanate were added to the mixture, followed by further stirring at room temperature for a period of two hours. The resulting mixture was then cooled in an ice-bath, and thereafter diluted with 125 ml. of ice water and filtered to afford a filtrate that was subsequently acidified with 6 N hydrochloric acid. The thick gummy material which formed at this point was then separated from the aqueous phase by means of decantation and was subsequently triturated with diethyl ether to give a crystalline material. In this manner, there were obtained 3.7 g. of 3'-methyl-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 141.5–143° C. after one recrystallization from isopropanol.

Analysis.—Calcd. for $C_{17}H_{16}N_2O_2$ (percent): C, 72.83; H, 5.75; N, 10.00. Found (percent): C, 73.13; H, 5.83; N, 10.04.

EXAMPLE II

The procedure described in Example I was repeated using 1.15 g. (0.005 mole) of 1-ethyl-2-oxo-5,6-dichloroindole, 0.264 g. (0.0055 mole) of sodium hydride (a 50% dispersion in mineral oil), 0.655 g. (0.0055 mole) of phenyl isocyanate and 15 ml. of dry N,N-dimethylformamide. In this particular case, the corresponding product obtained was 1 - ethyl - 2 - oxo-5,6-dichloro-2,3-dihydroindole-3-carboxanilide (1.6 g.), M.P. 194–195° C. after recrystallization from isopropanol.

Analysis.—Calcd. for $C_{17}H_{14}Cl_2N_2O_2$ (percent): C, 58.47; H, 4.04; N, 8.02. Found (percent): C, 58.57; H, 3.83; N, 7.93.

This particular compound was tested for anti-inflammatory activity in rats, using the carregeenin-induced rat foot edema test, and found to be active orally at levels of 33 mg./kg., 10 mg./kg., 3.0 mg./kg. and 1.0 mg./kg., respectively.

EXAMPLE III

The procedure described in Example I was repeated to prepare the following 2-oxo-2,3-dihydroindole-3-carboxanilides, starting from the corresponding 2-oxo-2,3-dihydroindole and appropriate phenyl isocyanate reagent in each case:

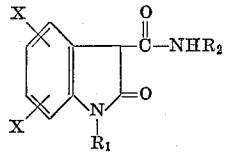
1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 153.5–155.5° C.
2'-chloro-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 188–190.5° C.
4'-methoxy-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 171–172° C.
3'-chloro-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 139–141° C.
4'-methyl-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 176–177° C.
2'-methyl-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 166–167.5° C.
4'-fluoro-1-methyl-2-oxo-5-chloro-2,3-dihydronidole-3-carboxanilide, M.P. 163–165° C.
4'-chloro-1-methyl-2-oxo-5-fluoro-2,3-dihydroindole-3-carboxanilide, M.P. 172–173° C.
4'-fluoro-1-methyl-2-oxo-5-fluoro-2,3-dihydroindole-3-carboxanilide, M.P. 184–185° C.
4'-chloro-1-ethyl-2-oxo-5-chloro-2,3-dihydroindole-3-carboxanilide, M.P. 170–171° C.
2'-fluoro-1-methyl-2-oxo-5-chloro-2,3-dihydroindole-3-carboxanilide, M.P. 184–185° C.
4'-bromo-1-methyl-2-oxo-5-chloro-2,3-dihydroindole-3-carboxanilide, M.P. 219–220° C.
4'-bromo-1-ethyl-2-oxo-5-chloro-2,3-dihydronidole-3-carboxanilide, M.P. 170–171° C.
4'-bromo-1-(n-propyl)-2-oxo-5-chloro-2,3-dihydroindole-3-carboxanilide, M.P. 160–162° C.
4'-bromo-1-ethyl-2-oxo-5-bromo-2,3-dihyroindole-3-carboxanilide, M.P. 150–153° C.
4'-fluoro-1-ethyl-2-oxo-5-bromo-2,3-dihydroindole-3-carboxanilide, M.P. 138–140° C.
2'-fluoro-1-ethyl-2-oxo-5-bromo-2,3-dihydroindole-3-carboxanilide, M.P. 176–178° C.
4'-chloro-1-methyl-2-oxo-5-bromo-2,3-dihydroindole-3-carboxanilide, M.P. 224–225° C.
2'-fluoro-1-methyl-2-oxo-5-bromo-2,3-dihydroindole-3-carboxanilide, M.P. 119.5–200.5° C.
4'-fluoro-1-methyl-2-oxo-5-bromo-2,3-dihydroindole-3-carboxanilide, M.P. 201–202° C.
4'-methoxy-1-ethyl-2-oxo-5-bromo-2,3-dihydrodinole-3-carboxanilide, M.P. 179–181° C.
4'-chloro-1-ethyl-2-oxo-5-fluoro-2,3-dihydroindole-3-carboxanilide, M.P. 154–156° C.
4'-bromo-1-ethyl-2-oxo-5-fluoro-2,3-dihydroindole-3-carboxanilide, M.P. 152–155° C.
2'-fluoro-1-ethyl-2-oxo-5-fluoro-2,3-dihydroindole-3-carboxanilide, M.P. 160–162° C.
4'-fluoro-1-ethyl-2-oxo-5-fluoro-2,3-dihydroindole-3-carboxanilide, M.P. 147–148° C.
4'-methoxy-1-ethyl-2,-oxo-5-fluoro-2,3-dihydroindole-3-carboxanilide, M.P. 159–162° C.
4'-fluoro-1-methyl-2-oxo-6-fluoro-2,3-dihydroindole-3-carboxanilide, M.P. 215.5–216.5° C.
2'-fluoro-1-methyl-2-oxo-6-chloro-2,3-dihydroindole-3-carboxanilide, M.P. 211–212° C.
4'-chloro-1-methyl-2-oxo-6-chloro-2,3-dihydroindole-3-carboxanilide, M.P. 225.5–266.5° C.
2'-fluoro-1-methyl-2-oxo-4-chloro-2,3-dihydroindole-3-carboxanilide, M.P. 194–196° C.
4'-chloro-1-ethyl-2-oxo-5-bromo-2,3-dihydroindole-3-carboxanilide, M.P. 190–191° C.
2'-chloro-1-ethyl-2-oxo-5-bromo-2,3-dihydroindole-3-carboxanilide, M.P. 192–193° C.
2'-fluoro-1-ethyl-2-oxo-5-methyl-2,3-dihydroindole-3-carboxanilide, M.P. 149–150° C.
4'-methoxy-1-ethyl-2-oxo-5-methyl-2,3-dihydroindole-3-carboxanilide, M.P. 206–207.5° C.
4'-fluoro-1-ethyl-2-oxo-5-bromo-2,3-dihydroindole-3-carboxanilide, M.P. 151–152° C.
4'-trifluoromethoxy-1-ethyl-5-methyl-2,3-dihydroindole-3-carboxanilide, M.P. 158–159° C.
4'-fluoro-1-ethyl-2-oxo-6-bromo-2,3-dihydroindole-3-carboxanilide, M.P. 190–191.5° C.
4'-fluoro-1-ethyl-2-oxo-5-methyl-2,3-dihydroindole-3-carboxanilide, M.P. 110–115° C.
4'-bromo-1-ethyl-2-oxo-6-bromo-2,3-dihydroindole-3-carboxanilide, M.P. 230–231° C.
2'-fluoro-1-ethyl-2-oxo-6-bromo-2,3-dihydroindole-3-carboxanilide, M.P. 214–215° C.
4'-chloro-1-ethyl-2-oxo-5,6-dichloro-2,3-dihydroindole-3-carboxanilide, M.P. 206–207° C.
4'-fluoro-1-ethyl-2-oxo-5,6-dichloro-2,3-dihydroindole-3-carboxanilide, M.P. 200.5–202° C.
4'-chloro-1-methyl-2-oxo-5-methoxy-2,3-dihydroindole-3-carboxanilide, M.P. 202.5–204° C.
4'-bromo-1-methyl-2-oxo-5-methoxy-2,3-dihydroindole-3-carboxanilide, M.P. 207.5–209° C.

4'-fluoro-1-methyl-2-oxo-5-methoxy-2,3-dihydroindole-3-carboxanilide, M.P. 182–183° C.

4'-methoxy-1-ethyl-2-oxo-5,6-dichloro-2,3-dihydroindole-3-carboxanilide, M.P. 201–202° C.

EXAMPLE IV

The procedure described in Example I is employed once again to prepare the following 2-oxo-2,3-dihydroindole-3-carboxamides, starting from the corresponding 2-oxo-2,3-dihydroindole compound and appropriate organic isocyanate reagent in each case:



X	Y	R_1	R_2
H	H	n-C_6H_{13}	2,4-difluorophenyl.
5-OC_2H_5	6-OC_2H_5	$C_6H_5CH_2$	3-bromophenyl.
5-Cl	H	n-C_3H_7	2-CF_3phenyl.
5-Cl	6-F	Allyl	2,5-dimethoxyphenyl
H	H	CH_2CF_3	2-ethylphenyl.
4-C_2H_5	H	$C_6H_5(CH_2)_2$	Phenyl.
5-Cl	6-Cl	n-C_4H_9	α-Naphthyl.
5-C_2H_5	6-C_2H_5	$C_6H_5(CH_2)_3$	β-Naphthyl.
4-OCF_3	H	Hydrogen	4-CF_3Ophenyl.
H	6-OCH_3	iso-C_5H_{11}	2-chlorophenyl.
5-Cl	6-Cl	n-C_3H_7	3-chlorophenyl.
4-F	H	$C_6H_5CH_2$	4-chlorophenyl.
4-(n-C_4H_9)	H	Methallyl	2-methylphenyl.
5-OC_2H_5	H	iso-C_3H_7	3-methylphenyl.
H	7-OCF_3	$C_6H_5(CH)_3$	4-methylphenyl.
5-Cl	H	CH_2CF_3	2-methoxyphenyl.
H	H	CH_3	3-thioethoxyphenyl
5-F	H	Allyl	4-methoxyphenyl.
5-CH_3	6-CH_3	n-C_4H_9	2,5-dichlorophenyl.
5-OCH_3	6-OCH_3	Hydrogen	3,4-dimethylphenyl.
H	H	iso-C_4H_9	3,4-dichlorophenyl.
H	7-Cl	CH_3	4-(n-butyl)phenyl.
H	H	Methallyl	3-CF_3phenyl.
4-CH_3	H	CH_2CF_3	2,4-dimethoxyphenyl.
H	7-(niC_4H_9)	$C_6H_5CH_2$	2,5-dimethoxyphenyl.
H	H	iso-C_3H_7	2-ethoxyphenyl.
5-OC_5H_{11}(n)	6-OC_5H_{11}(n)	Allyl	4-ethoxyphenyl.
H	H	CH_2CF_3	3-isopropoxyphenyl.
5-F	H	n-C_5H_{11}	Phenyl.
4-(n-C_5H_{11})	H	Methallyl	α-Naphthyl.
4-Cl	7-Cl	C_2H_5	β-Naphthyl.
H	6-CF_3	CH_3	2-thiomethoxyphenyl.
5-F	6-F	$C_6H_5(CH_2)_2$	4-bromophenyl.
H	H	n-C_6H_{13}	4-fluorophenyl.
4-Cl	H	Hydrogen	4-CF_3phenyl.
5-CF_3	6-CF_3	$C_6H_5CH_2$	2,3-dichlorophenyl.
5-Cl	H	CH_2CF_3	5-Cl-2-methoxyphenyl.
5-Cl	6-Cl	iso-C_4H_9	3,5-dichlorophenyl.
4-CF_3	H	$C_6H_5CH_2$	3,5-dimethoxyphenyl.
H	H	n-C_5H_{11}	4-thiopropoxyphenyl.
H	6-OC_6H_{11}(n)	Methallyl	2,6-dimethylphenyl.
5-(n-C_5H_{11})	6-(n-C_5H_{11})	CH_3	2-CH_3O-5-methylphenyl.
H	H	$C_6H_5(CH_2)_2$	3-Cl-4-methylphenyl.
5-OCF_3	6-OCF_3	n-C_6H_{13}	2,4-dimethylphenyl.
4-OCH_3	H	C_2H_5	2-Cl-5-CF_3phenyl.
H	6-F	Hydrogen	3-CF_3Ophenyl.
4-Br	H	n-C_6H_{13}	3,5-difluorophenyl.
5-Cl	6-Cl	CH_3	Phenyl.
H	H	n-C_6H_{13}	Phenyl.
5-Br	6-Br	C_2H_5	3-chlorophenyl.
5-Br	H	Allyl	2-methoxyphenyl.
H	H	n-C_6H_{13}	2-methylphenyl.
4-Cl	7-Cl	n-C_6H_{13}	Phenyl.
5-Br	H	iso-C_3H_7	2,5-difluorophenyl.
H	H	n-C_6H_{13}	4-chlorophenyl.
4-Br	H	$C_6H_5CH_2$	4-chlorophenyl.
5-Cl	6-Br	Allyl	3-methoxyphenyl.
4-Cl	H	n-C_6H_{13}	2,4-difluorophenyl.
H	6-Br	$C_6H_5(CH_2)_2$	4-methylphenyl.
H	7-Br	n-C_6H_{13}	α-Naphthyl.
4-Br	7-Br	C_2H_5	β-Naphthyl.

EXAMPLE V

A solution consisting of 1.75 g. (0.0075 mole) of ethyl 1-ethyl-2-oxo-2,3 - dihydroindole - 3 - carboxylate and 1.42 g. (0.00825 mole) of p-bromoaniline dissolved in 70 ml. of xylene was heated to the boiling point and then slowly distilled so as to remove 60 ml. of the solvent therefrom. At this point, 40 ml. of fresh xylene solvent were added to the mixture and distillation was thereafter continued until the same amount of said solvent was also removed. Upon completion of this step, the reaction solution was cooled to room temperature and a crystalline precipitate was soon observed to form. The latter material was subsequently collected by means of suction filtration and washed dry with di-isopropyl ether to afford 2.0 g. of 4'-bromo-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 175–175.5° C. (with softening at 150° C.) after one recrystallization from cyclohexane.

Analysis.—Calcd. for $C_{17}H_{15}BrN_2O_2$ (percent): C, 56.84; H, 4.21; N, 7.80. Found (percent): C, 57.10; H, 4.31; N, 7.86.

EXAMPLE VI

The procedure described in Example V was repeated to prepare the following 2-oxo-2,3-dihydroindole-3-carboxanilides, starting from the corresponding ethyl 2-oxo-2,3-dihydroindole - 3 - carboxylate and the appropriate aniline compound in each instance:

2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 218–219.5° C.

4'-chloro-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 229.5–231° C.

2',4'-dichloro-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 269° C. (decomp.).

2'-chloro-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 224–225° C.

4'-methoxy-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 215.5–217.5° C.

2'-methoxy-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 208.5–210° C.

3'-trifluoromethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 196–198° C.

2'4'-dimethoxy-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 218–219° C.

3'-methoxy-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 168° C.

2',3'-dichloro-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 241° C. (decomp.)

3',4'-dichloro-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 238.5° C. (decomp.)

3',5'-dichloro-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 236° C. (decomp.)

2',5'-difluoro-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 204.5–205.5° C.

2'-methoxy-5'-chloro-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 190–191° C.

3',5'-dichloro-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 202–203° C.

3',4'-dichloro-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 181.5–182.5° C.

2,5-dichloro-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 206.5–207.5° C.

2',3'-dichloro-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 194–195° C.

2',4'-dichloro-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 219–220.5° C.

4'-chloro-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 194.5–195° C.

2',6'-dichloro-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 205° C. (decomp.)

2',4'-difluoro-1-methyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 170–171° C.

2',3'-dichloro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 125–126.5° C.

2',5'-dichloro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 153–154° C.

2'5'-difluoro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 153.5–155° C.

3',4'-dichloro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 163.5–165° C.

2',4'-dichloro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 166–167° C.

2'-chloro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 123–124° C.

4'-methoxy-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 142.5–143.5° C.

2',6'-dichloro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 131–148° C.
2',4'-difluoro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 148.5–149.5° C.
3'-chloro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 127.5–128.5° C.
4'-chloro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 165–166° C.
2'-methoxy-5'-chloro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 175–176° C.
3',5'-dichloro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 175.5–177° C.
3'-trifluoromethyl-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 149–150° C.
4'-fluoro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 135.5–136.5° C.
2'-fluoro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 137–138.5° C.
2'-bromo-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 99–100° C.
3'-bromo-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 150–151° C.
2'-methyl-4'-nitro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 167° C. (melts slowly)
3'-chloro-4'-fluoro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 170–171° C.
3'-chloro-4'-methoxy-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 170–171° C.
3'-fluoro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 139–140° C.
2',4'-difluoro-1-(n-propyl)-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 162–165° C.
3',4'-dichloro-1-(n-propyl)-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 144–145° C.
2',5'-dichloro-1-(n-propyl)-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 144–145° C.
4'-chloro-1-(n-propyl)-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 139–141° C.
2',3'-dichloro-1-(n-propyl)-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 128–130° C.
2',4'-dichloro-1-(n-propyl)-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 132–134° C.
2'-chloro-1-(n-propyl)-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 122–124° C.
2',5'-difluoro-1-(n-propyl)-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 170–171° C.
3'-fluoro-1-(n-propyl)-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 139–140° C.
2'-methoxy-5'-chloro-1-(n-propyl)-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 147–148° C.
3',5'-dichloro-1-(n-propyl)-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 144–145° C.
2'-fluoro-1-(n-propyl)-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 159–161° C.
4'-fluoro-1-(n-propyl)-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 135–137° C.

EXAMPLE VII

The procedure described in Example V is repeated once again, only this time to prepare the same 2-oxo-2,3-dihydroindole-3-carboxamides previously reported in Example IV. In each instance, the corresponding ethyl 2-oxo-2,3-dihydro-3-carboxylate and the appropriate organic amine reagent of choice are the proper starting materials employed for the present purposes at hand.

EXAMPLE VIII

A slurry of 0.24 g. (0.005 mole) of sodium hydride (a 50% dispersion in mineral oil) in 20 ml. of hexamethylphosphoramide was prepared and subsequently treated with 1.05 g. (0.005 mole) of 1-(n-propyl)-2-oxo-5-chloro-2,3-dihydroindole. To the resulting suspension, there were then added with stirring 1.78 g. (0.0055 mole) of N,N-diphenyl-N'-(2,4-difluorophenyl)urea in a dropwise manner during the course of a 15-minute period. The resulting solution was then stirred at room temperature (~25° C.) for a period of 3.5 hours, at which point thin-layer chromatography showed the reaction to be essentially complete. Upon dilution with water, a precipitate formed and the aqueous phase was then separated by means of filtration and subsequently extracted with diethyl ether to remove diphenylamine by-product. The resulting aqueous solution was then made acidic with 6 N hydrochloric acid and again extracted with diethyl ether. After drying the ethereal extracts over anhydrous sodium sulfate and filtering, there was obtained a clear ethereal filtrate that subsequently gave 1.7 g. of a yellow semi-solid on evaporation to near dryness under reduced pressure. Recrystallization of the latter material from aqueous ethanol then afforded 0.40 g. of 2',4'-difluoro-1-(n-propyl)-2-oxo-5-chloro-2,3-dihydroindole-3-carboxanilide, M.P. 118–120° C. The melting point was raised to 122–123° C. after further recrystallization from n-pentane.

Analysis.—Calc'd for $C_{18}H_{15}ClF_2N_2O_2$ (percent): C, 59.26; H, 4.14; N, 7.68. Found (percent): C, 59.02; H, 4.24; N, 7.47.

EXAMPLE IX

The procedure described in Example VIII was repeated using 2.4 g. (0.01 mole) of 1-ethyl-2-oxo-5-bromo-2,3-dihydroindole, 3.56 g. (0.011 mole) of N,N-dihpenyl-N'-(2,4-difluorophenyl)urea, 0.53 g. (0.011 mole) of sodium hydride (a 50% dispersion in mineral oil) and 20 ml. of hexamethylphopshoramide In this particular case, the corresponding product obtained was 2',4'-difluoro-1-ethyl-2-oxo-5-bromo-2,3-dihydroindole - 3 - carboxanilide (1.3 g.), M.P. 155–156° C. after recrystallization from cyclohexane.

Analysis.—Calcd. for $C_{17}H_{13}BrF_2N_2O_2$ (percent): C, 51.66; H, 3.31; N, 7.09. Found (percent): C, 51.14; H, 3.35; N, 6.84.

This particular compound was tested for anti-inflammatory activity in rats, using the carregeenin-induced rat foot edema test, and found to be active orally at dose levels of 33 mg./kg., 10 mg./kg., 3.0 mg./kg. and 1.0 mg./kg, respectively

EXAMPLE X

The procedure described in Example VIII was repeated to prepare the following 2-oxo-2,3-dihydroindole-3-carboxanilides, starting from the corresponding 2-oxo-2,3 - dihydroindole and appropriate N,N - diphenyl - N'-phenylurea reagent in each instance:

2',4'-difluoro-1-ethyl-2-oxo-2,3-dihydroindole-3-carboxanilide, MP. 148.5–149.5° C.
2',4'-difluoro-2-oxo-5-chloro-2,3-dihydroindole-3-carboxanilide, M.P. 180–181° C.
2',4'-difluoro-1-methyl-2-oxo-5-chloro-2,3-dihydroindole-3-carboxanilide, M.P. 204–205° C.
2',4'-difluoro-1-ethyl-2-oxo-5-chloro-2,3-dihydroindole-carboxanilide, M.P. 161–162° C.
2',4'-difluoro-1-methyl-2-oxo-5-fluoro-2,3-dihydroindole-3-carboxanilide, M.P. 163–164° C.
3'-fluoro-1-methyl-2-oxo-5-chloro-2,3-dihydroindole-3-carboxanilide, M.P. 158–160° C.
2',4'-difluoro-2-oxo-2,3-dihydroindole-3-carboxanilide, M.P. 173–175° C.
2',4'-difluoro-1-ethyl-2-oxo-5-fluoro-2,3-dihydroindole-3-carboxanilide, M.P. 167–168° C.
2',4'-difluoro-1-methyl-2-oxo-5-bromo-2,3-dihydroindole-3-carboxanilide, M.P. 211.5–213° C.
2',4'-difluoro-1-methyl-2-oxo-6-chloro-2,3-dihydroindole-3-carboxanilide, M.P. 205.5–207° C.
3'-fluoro-1-ethyl-2-oxo-5-methyl-2,3-dihydroindole-3-carboxanilide, M.P. 137–138° C.
2',4'-difluoro-1-ethyl-2-oxo-5-methyl-2,3-dihydroindole-3-carboxanilide, M.P. 129–130° C.
2',4'-difluoro-1-ethyl-2-oxo-6-bromo-2,3-dihydroindole-3-carboxanilide, M.P. 211–212° C.
2',4'-difluoro-1-methyl-2-oxo-5-methoxy-2,3-dihydroindole-3-carboxanilide, M.P. 194–195.5° C.

EXAMPLE XI

The procedure described in Example VIII is repeated once again, only this time to prepare the same 2-oxo-2,3-dihydroindole-3-carboxamides previously reported in Example IV. In each instance, the corresponding 2-oxo-2,3-dihydroindole compound and the appropriate N,N-diphenylurea derivative of choice (i.e., 1,1,3-trisubstituted urea) are the proper starting materials employed for the present purposes at hand.

EXAMPLE XII

The sodium salt of 2',4' - difluoro - 1 - ethyl-2-oxo - 5-bromo-2,3-dihydroindole-3-carboxanilide is prepared by dissolving said compound in anhydrous methanol and then adding said solution to another methanolic solution which contains an equivalent amount in moles of sodium methoxide. Upon subsequent evaporation of the solvent therefrom via freezing-drying, there is obtained the desired alkali metal salt in the form of an amorphous solid powder which is freely soluble in water.

In like manner, the potassium and lithium salts are also prepared as are the alkali metal salts of all the other acidic 2-oxo-2,3-dihydroindole-3-carboxamides of this invention, which were reported previously in the preceding Examples.

EXAMPLE XIII

The calcium salt of 1-ethyl-2-oxo-5,6-dichloro-2,3-dihydroindole-3-carboxanilide is prepared by dissolving said compound in water containing an equivalent amount in moles of calcium hydroxide and then freeze-drying the mixture. The corresponding magnesium salt is also prepared in like manner, as are all the other alkaline-earth metal salts not only of this compound, but also of those acidic 2-oxo-2,3-dihydroindole-3-carboxamides described in the examples immediately preceding Example XII.

EXAMPLE XIV

A dry solid pharmaceutical composition is prepared by blending the following materials together in the proportions by weight specified below:

2',4' - difluoro - 1 - ethyl - 2 - oxo - 5 - bromo - 2,3-dihydroindole-3-carboxanilide	50
Sodium citrate	25
Alginic acid	10
Polyvinylpyrrolidone	10
Magnesium stearate	5

After the dried composition is thoroughly blended, tablets are punched from the resulting mixture, each tablet being of such size that it contains 100 mg. of the active ingredient. Other tablets are also prepared in a similar manner containing 5, 10, 25 and 50 mg. of the active ingredient, respectively, by merely using the appropriate amount of the 2-oxo-2,3-dihydroindole compound in each case.

EXAMPLE XV

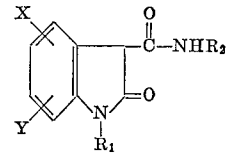
A dry solid pharmaceutical composition is prepared by combining the following materials together in the proportions by weight indicated below:

1 - ethyl - 2 - oxo - 5,6 - dichloro - 2,3 - dihydroindole-3-carboxanilide	50
Calcium carbonate	20
Polyethylene glycol, average molecular weight 4000	30

The dried solid mixture so prepared is then thoroughly agitated so as to obtain a powdered product that is completely uniform in every respect. Soft elastic and hard-filled gelatin capsules containing this pharmaceutical composition are then prepared, employing a sufficient quantity of material in each case so as to provide each capsule with 250 mg. of the active ingredient.

What is claimed is:

1. An oxindolecarboxamide compound of the formula:



and the base salts thereof with pharmacologically acceptable cations, wherein X and Y are each a member selected from the group consisting of hydrogen, fluorine, chlorine, bromine, alkyl and alkoxy each having from one to five carbon atoms, trifluoromethyl and trifluoromethoxy; R_1 is a member selected from the group consisting of hydrogen, 2,2,2 - trifluoroethyl, alkyl having from one to six carbon atoms, alkenyl having up to four carbon atoms and phenylalkyl having up to three carbon atoms in the alkyl moiety; and R_2 is a member selected from the group consisting of naphthyl, phenyl, and mono- and di-substituted phenyl wherein each substituent is chosen from the group consisting of fluorine, chlorine and bromine, alkyl having up to four carbon atoms, alkoxy and thioalkoxy and each having up to three carbon atoms, trifluoromethyl and trifluoromethoxy.

2. A compound as claimed in claim 1 wherein X and Y are each hydrogen, R_1 is alkyl or from one to six carbon atoms and R_2 is phenyl.

3. A compound as claimed in claim 1 wherein X and Y are each hydrogen, R_1 is alkyl of from one to six carbon atoms and R_2 is chlorophenyl.

4. A compound as claimed in claim 1 wherein X and Y are each hydrogen, R_1 is alkyl of from one to six carbon atoms and R_2 is fluorophenyl.

5. A compound as claimed in claim 1 wherein X and Y are each hydrogen, R_1 is alkyl of from one to six carbon atoms and R_2 is difluorophenyl.

6. A compound as claimed in claim 1 wherein X and Y are each hydrogen, R_1 is alkyl of from one to six carbon atoms and R_2 is tolyl.

7. A compound as claimed in claim 1 wherein X and Y are each hydrogen, R_1 is hydrogen and R_2 is dichlorophenyl.

8. A compound as claimed in claim 1 wherein X is chlorine, Y is hydrogen, R_1 is alkyl of from one to six carbon atoms and R_2 is difluorophenyl.

9. A compound as claimed in claim 1 wherein X is bromine, Y is hydrogen, R_1 is alkyl of from one to six carbon atoms and R_2 is difluorophenyl.

10. A compound as claimed in claim 1 wherein and Y are each chlorine, R_1 is alkyl of from one to six carbon atoms and R_2 is phenyl.

11. 2',4'-difluoro-1-ethyl-2-oxo-5-bromo-2,3 - dihydroindole-3-carboxanilide.

12. 1-ethyl-2-oxo-5,6-dichloro-2,3-dihydroindole-3 - carboxanilide.

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