

PATENT SPECIFICATION

NO DRAWINGS

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Int. Cl: —C 07 d 31/42

COMPLETE SPECIFICATION

Substituted Nicotinic Acids and Method for the Manufacture thereof

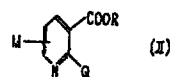
We, SCHERICO LTD., of Topferstrasse 5, Lucerne, Switzerland, a body corporate constituted under the laws of Switzerland, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to 2-anilino-nicotinic acid derivatives, to pharmaceutical compositions containing such compounds and to processes for making such compounds and compositions.

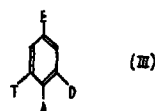
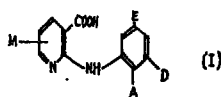
The invention provides novel chemical compounds having the general formula:

hereinafter referred to as 'functional derivatives'.

The above mentioned novel compounds may be produced by reacting together an appropriate nicotinic acid compound of the general formula



with an appropriate compound of the general formula



and their pharmaceutically acceptable salts, esters, for example lower alkyl esters, and hydroxamic acid derivatives, wherein M is hydrogen or lower alkyl; one of A and E is hydrogen and the other is chlorine or bromine; and D is chlorine or bromine or, when A is chlorine and E is H, then D may also be methyl with an additional chlorine substituent at the 6-position of the phenyl ring.

Included within pharmaceutically acceptable salts are metal, for example alkali metal, and ammonium or substituted ammonium salts (such as for instance the diethanolamine salts) of the aforementioned anilino-nicotinic acids. By the term 'lower alkyl' is meant alkyl groups having up to 4 carbon atoms. The pharmaceutically acceptable salts, esters and hydroxamic acid derivatives are

in which formulae R is hydrogen or a substituent which does not interfere with the desired reaction, A, D, E, and M have the same meaning as above, one of Q and T is an unsubstituted or benzyl-, alkyl- or acyl-monosubstituted amino group and the other is a group capable of reacting with the amino group with the elimination of hydrogen therefrom to form the nitrogen bridge between the phenyl moiety and the pyridine moiety of the compound of formula I. Q may be for instance a halogen atom, an alkoxy, alkylthio, alkoxy-sulfonyl, or nitro group, with T being unsubstituted or benzyl-, alkyl-, or acyl-monosubstituted amino group, or T may be for instance a halogen atom with Q being an unsubstituted or monosubstituted amino group. It is obvious that

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other, chemically equivalent groups can be used likewise. If necessary, any substituent being attached to the nitrogen atom is subsequently removed, e.g. by catalytic reduction procedures. For the preparation of the functional derivatives of the compounds of the general formula I there may in certain cases (e.g. with the esters) be used the appropriately connected or substituted starting compounds, or the desired conversion or substitution may be subsequently effected in the 2-anilino-nicotinic acids according to known methods. Preferably the reaction is carried out in the presence of copper powder and/or alkali metal carbonate. The compounds of the invention may be used for treating and alleviating inflammation and inflammatory conditions by administering a therapeutically effective quantity of a novel compound of this invention. Novel compounds of this invention may be used to cause an analgesic effect. Pharmaceutical compositions containing the novel compounds of this invention, may also contain other active compounds having anti-inflammatory properties, such, for example, as phenyl butazone, acetyl-salicylic acid or a steroid such as betamethasone. Pharmaceutical compositions according to the invention may be prepared by admixing a compound of the invention with a carrier and, if desired, another active compound having anti-inflammatory properties.

The compounds of the invention, in the form of the free acid or non-toxic salt thereof, possess the inherent applied use characteristics of exerting an anti-inflammatory response as determined by pharmacological evaluation, and also exert an analgesic action. They are thus useful in treating inflammation and at higher doses in treating certain symptoms of pain.

The treatment of inflammation with concomitant absence of side effects induced by the anti-inflammatory agent has been a goal long sought. In general, steroids having cortisone-like activity have been employed for this purpose. The use of steroid therapy suffers from the drawback of side effects induced by the corticoid such as electrolyte imbalance, water retention and the like. Our novel compounds are rather specific in their action and are non-steroidal in character, thus the side effects due to steroid therapy are eliminated. It is also known that non-steroidal compounds employed in the treatment of inflammatory conditions have been found to exhibit deleterious side effects, such as—for example—ulceration of the gastrointestinal tract. By the employment of standard laboratory techniques the novel compounds of this invention have demonstrated a marked lessening of this ulcerative effect and thus, although the anti-inflammatory compounds of this invention may demonstrate less potency than other previously used compounds the lack of the aforementioned side effects enhances the

functional-use indices of the novel compounds of this invention.

Those compounds of the invention having a free carboxylic group are preferably prepared by heating together a 2-halo- (preferably chloro- or bromo-) nicotinic acid with an appropriately substituted aniline, said heating taking place either in a high boiling solvent such as xylene or cymene, or by merely melting the reactants in the presence of each other. In the melt procedure, the reaction temperature will rise as the reaction proceeds. The reaction is completed generally after 15—30 minutes as evidenced by a fall in reaction temperature. The fused melt is then treated with dilute aqueous base, for example sodium carbonate or sodium hydroxide, and extracted with a water immiscible solvent. The product, in the form of a soluble salt, is in the aqueous layer and is precipitated therefrom by acidifying with dilute mineral acid and the desired compound is filtered off.

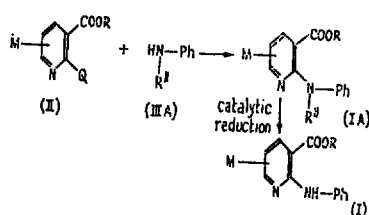
During the course of the reaction, for each mole of reaction product there is formed a mole of hydrogen halide. Accordingly, it is preferred to employ two moles of the substituted aniline for each mole of the 2-halonicotinic acid reactant. The extra mole of the former readily takes up the hydrogen halide formed in the form of an acid addition salt.

Alternatively, there may be employed an ester (preferably lower alkyl) of the halogeno nicotinic acid. The ester group may subsequently be hydrolyzed, if a 2-anilino-nicotinic acid with a free carboxylic group is desired. (During the reaction with the substituted aniline, hydrolysis may occur but the alcohol produced thereby is easily removed during the purification).

In addition to the use of the reactants in the above described nucleophilic displacement reaction, other equivalently functioning reactants may be employed to produce the desired novel compositions of this invention. For example, instead of employing a 2-halonicotinic acid (or ester thereof) a nicotinic acid (or ester thereof) having an alkoxy, alkylthio, alkoxysulfonyl, nitro, or other equivalently functioning substituent in the 2-position thereof may be so employed. In such instances, the same reaction conditions used in the previously described nucleophilic displacement reaction would be employed.

Alternatively, instead of employing the previously described anilines, an N-substituted aniline reactant may be heated with the foregoing 2-substituted nicotinic acids (or esters thereof). Such equivalently functioning N-substituted aniline reactants include those anilines being accordingly substituted in the phenyl moiety and wherein a hydrogen atom attached to the nitrogen atom has been replaced with substituents such as benzyl, alkyl

or acyl. Again, in the use of these equivalently functioning reactants the previously described nucleophilic displacement reaction conditions would be employed. In those instances wherein the N-substituted aniline reactant has been employed, the 2-(N-substituted anilino)-nicotinic acid (or ester thereof) may be subjected to catalytic reduction procedures to remove the alkyl, benzyl or acyl radical from the nitrogen atom. The foregoing reaction may be illustrated by the following schematic representation:

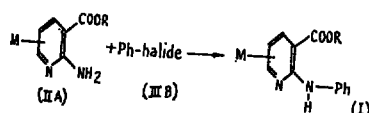


wherein M is either hydrogen or lower alkyl, Q may be for instance a halogen atom, an alkoxy, alkylthio, alkoxysulfonyl, or nitro group, R may be hydrogen or a functional substituent which does not interfere with the desired reaction, such as an ester group or potassium atom, R' may be alkyl, acyl or benzyl, and Ph represents a substituted phenyl of the following formula



wherein A, D, and E are as defined above. Additionally, the compounds embraced within the concepts of this invention may also be prepared from 2-amino-nicotinic acids (or, for example, the esters and potassium salts thereof) by means of a nucleophilic displacement reaction with an appropriately substituted phenyl halide. As in the previously described nucleophilic displacement reaction the preparation may be effected for instance by heating the reactants together in a sealed tube, either in a high boiling solvent such as xylene or cymene or by merely melting the reactants in the presence of each other.

The foregoing reaction may be illustrated by the following schematic representation:



wherein M, R, and Ph are as previously

defined. If desired, the so obtained compounds may be transformed according to known methods into the corresponding functional derivatives, namely lower alkyl esters, pharmaceutically acceptable salts (such as for instance the diethanolamine salt) and hydroxamic acid derivatives.

The compounds prepared according to the foregoing procedures are, in general, crystalline solids which may be purified by crystallization from aqueous alcohol, benzene, ethylacetate, isopropanol, or other appropriate solvents.

Representative of the aniline reactants are 2,3-dichloroaniline, 2,3-dibromoaniline, 3,5-dibromoaniline, 3,5-dichloroaniline, as well as those required to prepare the hereinafter described equivalently functioning anilino-nicotinic acids.

The preferred nicotinic acids which are utilizable in this reaction are 2-chloro- (or bromo-) nicotinic acid and alkyl substitution products thereof such as 2-chloro-6-methyl-nicotinic acid and other readily available or preparable 2-halogeno-lower-alkyl-nicotinic acids.

Anti-inflammatory therapy by means of adrenocorticosteroids is sometimes limited in its application in view of certain hormonal side effects. The anilino nicotinic acids of this invention are apparently free of such hormonal side effects.

It is known that the potencies of drugs in delaying the appearance of erythema on the skin of albino guinea pigs subjected to irradiation with ultra-violet light are closely correlated with their potencies as anti-inflammatory agents. The U.V. erythema test is a standard pharmacological test for determining anti-inflammatory activity. Certain agents exhibiting anti-inflammatory activity in this test are also analgesic with carry-over to different species having been demonstrated. Such agents include phenylbutazone, acetylsalicylic acid and 1-phenyl-2,3-dimethyl-pyrazolone.

We have found that the anilino-nicotinic acid derivatives described herein exhibit an activity as evidenced by the U.V. erythema test equal to or greater than that of the commonly used nonsteroid anti-inflammatory agent, phenylbutazone. Thus, the anilino-nicotinic acid derivatives described herein are useful in treating inflammation, especially that associated with rheumatoid and osteoporosis joint diseases, collagen diseases, bursitis, gouty arthritis, and spondylitis.

The anilino-nicotinic acid derivatives of this invention will elicit an anti-inflammatory response when administered in a dose range of about 100 to 500 mg. daily. In animals a dose of about 5 mg. per kg. body weight is sufficient to elicit an anti-inflammatory response. Of the compounds described herein, 2-(2,3-dichloroanilino)-nicotinic acid

appears to be the most potent especially in comparison with the standard phenylbutazone in protecting the animals against a lethal irradiation of ultra violet light. In addition, these compounds elicit an anti-pyretic effect demonstratable pharmacologically.

The pharmacological activity of the compounds of this invention appears to be critically dependent on structure. Shifting the carboxyl group such as would exist in a picolinic or isonicotinic acid moiety results in obliteration or extreme diminution of anti-inflammatory activity. The nature of the substituents and their position in the anilino moiety also appear important to maintain the proper degree of utility. As a general rule, unsubstituted or mono-substituted anilino-nicotinic acids appears to be either inactive or exhibit such a low order of activity as to be of no use. The compounds of the invention, however, have a high order of anti-inflammatory activity. The following compounds are particularly preferred: 2 - (2,3-dichloroanilino) - nicotinic acid, 2 - (3,5-dichloroanilino) - nicotinic acid and 2 - (2,6 - dichloro - 3 - methylanilino) - nicotinic acid.

The following examples are illustrative of the methods of synthesis of the compounds of this invention:

EXAMPLE 1

2-(2,3-dichloro anilino)-nicotinic acid

Mix 15.7 g. (0.1 mole) of 2-chloronicotinic acid with 32.4 g. (0.2 mole) of 2,3-dichloroaniline. Stir the mixture and heat to 120—130°C. (the temperature will rise to about 175—200°C as the reaction proceeds). After the reaction is completed as evidenced by a fall in temperature, cool the mass and triturate in dilute hydrochloric acid. Filter and wash the solid with water. Recrystallize from isopropyl acetate m.p. 250—251°C.

Alternatively, the compound of this example [2 - (2,3-dichloroanilino) - nicotinic acid] is prepared by heating together 30 g. of ethyl - 2 - chloronicotinate and 52.2 g. of 2,3 - dichloro - aniline at 200°C for 10 minutes. Cool, dissolve in 100 ml. hot ethanol, cool and filter obtaining the ethyl ester of this example.

Dissolve 32.6 g. of the ethyl ester in a solution of 13.25 g. of potassium hydroxide in 1 litre of methanol. Heat on a steam bath overnight allowing the methanol to evaporate. Dissolve the residue in water, acidify with dilute hydrochloric acid and filter obtaining the acid of this example.

Alternatively the 2-chloronicotinic acid may be replaced with equivalent quantities of 2-methoxy-nicotinic acid, 2-methyl-thionicotinic acid, 2-methoxysulfonylnicotinic acid, 2-nitro-nicotinic acid, and by following substantially the same procedures outlined in this example there is produced the desired 2 - (2,3 - dichloro - anilino) - nicotinic acid.

Similarly, the 2,3-dichloroaniline may be replaced by equivalent quantities of 3,5-dichloroaniline, 2 - chloro - 3 - bromoaniline, 3 - chloro - 5 - bromoaniline, 3,5-dibromoaniline, 2,6 - dichloro - 3 - methylaniline, and by reacting said aniline reactants with 2-chloronicotinic acid (or with the equivalently functioning nicotinic acid such as 2-bromonicotinic acid, 2-methoxynicotinic acid, 2-methylthionicotinic acid and 2-methoxysulfonylnicotinic acid or 2-nitronicotinic acid) substantially according to the procedures outlined for this example there is produced 2 - (3,5-dichloroanilino) - nicotinic acid, 2 - (2 - chloro - 3 - bromoanilino) - nicotinic acid, 2 - (3 - chloro - 5 - bromoanilino) - nicotinic acid, 2 - (3,5 - dibromo - anilino) - nicotinic acid, 2 - (2,6 - dichloro - 3 - methyl - anilino) - nicotinic acid respectively. In those instances wherein a particular reactant is not specifically described in the literature, such reactants may be prepared according to the methods used to prepare the known reactants suitable for the foregoing reactions.

The diethanolamine salts of the compounds set forth in formula (I) above may be prepared by a method analogous to that disclosed in Example 3 of our copending application No. 13779/68 (Serial No. 1147702).

EXAMPLE 2

2-(2,3-Dichloro-anilino)-nicotinic Acid

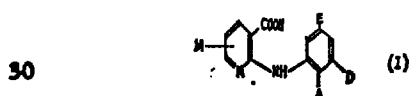
Mix 19.5 g. (0.1 mole) of potassium 2-chloronicotinate, 32.4 g. (0.2 mole) of 2,3-dichloroaniline, 1 g. of copper powder and 100 ml. of *n*-amyl alcohol. Stir and reflux for 6 hours. Cool, make alkaline with sodium bicarbonate solution. Steam-distil to remove unreacted 2,3-dichloroaniline. Cool the pot residue, filter and extract the filtrate with ether. Separate the aqueous phase, acidify and filter. Recrystallize from isopropyl acetate, m.p. 250—251°C.

The compounds of this invention are acids and indeed are soluble in aqueous alkali. The alkali metal salts of the novel compounds may be prepared by methods well known in the art for the preparation of a salt of a strong base with a weak acid. For example, the alkali metal salt, preferably the sodium salt, may be obtained by evaporation of an alkaline (with sodium hydroxide) solution of the anilino-nicotinic acid described herein. Alternatively, non-aqueous media may be employed. For example, by mixing together an alcoholic solution of an anilino-nicotinic acid with an alcoholic solution containing a stoichiometric quantity of an alkali metal alkoxide and evaporating the solvent, there is obtained the alkali metal salt which is soluble in water. In similar fashion and by other known techniques other functional derivatives, i.e. other pharmaceutically acceptable salts, are prepared. Representative of such salts are, in addition to the sodium salts,

- those wherein the cation is ammonium, or substituted ammonium (such as diethanol-ammonium), potassium, lithium, calcium and aluminium which advantageously allow for greater solubility or greater ease in formula-
 5 tion and are considered the full equivalent of the free carboxylic acid. Also included within this class of functional derivatives are the hydroxamic acid derivatives which
 10 are obtained by the condensation of an alkyl ester of the hereinabove described anilino nicotinic acids with hydroxylamine hydrochloride in the presence of sodium meth-
 15 oxide. The compositions described herein may be administered parenterally or enterally by incorporating them into dosage forms such as tablets, capsules, elixirs, solutions and sus-
 20 pensions. Representative embodiments of the formulations containing the 2 - methyl - 3 - chloroanilino analogues of the compounds of this invention are disclosed in our copend-
 25 ing Application No. 13779/68 (Serial No. 1147702). Similar formulations may be prepared containing the compounds of this inven-
 tion.

WHAT WE CLAIM IS:—

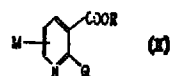
1. 2-Anilino-nicotinic acid compounds of the formula:



wherein M is hydrogen or lower alkyl; one of A and E is hydrogen and the other is chlorine or bromine; and D is chlorine or bromine or when A is chlorine and E is H
 35 then D may also be methyl with an additional chlorine substituent at the 6-position of the phenyl ring.

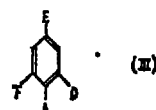
2. Compounds as claimed in claim 1, wherein D is chloro, M is hydrogen, and A and E have the same significance as indicated in claim 1.
 40 3. Compounds as claimed in claim 1, wherein A is hydrogen, D and E are chloro, and M has the same significance as in claim 1.
 45 4. 2-(2,3-Dichloroanilino)-nicotinic acid.
 5. 2-(3,5-Dichloroanilino)-nicotinic acid.
 6. 2 - (2,6 - Dichloro - 3 - methylanilino) - nicotinic acid.
 50 7. Pharmaceutically acceptable salts, esters and hydroxamic acid derivatives of the compounds claimed in claims 1 to 6.
 8. A salt as claimed in claim 7 which is an alkali metal salt.
 55 9. A salt as claimed in claim 7 which is a diethanolamine salt.
 10. Process for the production of a com-

pound claimed in claim 1 characterised in that a compound of the general formula:



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is condensed with a compound of the general formula:



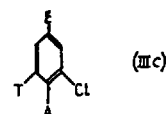
in which formulae R is a hydrogen atom or a substituent which does not interfere with the desired reaction, A, D, E and M are as defined in any of claims 1 to 8, one of Q and T is an unsubstituted or benzyl-, alkyl- or acyl-monosubstituted amino group and the other is a group capable of reacting with the amino group with the elimination of hydrogen therefrom to form the nitrogen bridge between the phenyl moiety and the pyridine moiety of the compounds of formula (I).
 75 80 85

11. Process as claimed in claim 10, wherein the symbol Q in the general formula (II) represents a halogen atom, an alkoxy, alkylthio, alkoxysulfonyl or nitro group, and the symbol T in the general formula (III) represents an unsubstituted or benzyl-, alkyl-, or acyl-monosubstituted amino group.
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12. Process as claimed in claim 10, wherein the symbol Q in the general formula (II) represents an unsubstituted or monosubstituted amino group and the symbol T in the general formula (III) represents a halogen atom.
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13. Process as claimed in any of claims 10 to 12 wherein R represents a hydrogen atom or an ester group or a potassium atom.
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14. Process as claimed in any one of claims 10 to 13, wherein the compounds of the general formula (II) in which M is a hydrogen atom, Q is a halogen atom, an alkoxy, alkylthio, alkoxysulfonyl or nitro group, and R is a hydrogen atom or an ester group, are reacted with compounds of the general formula
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wherein A and E have the same significance as in claim 1, and T is an amino group
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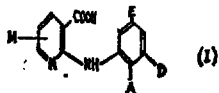


those wherein the cation is ammonium, or substituted ammonium (such as diethanol-ammonium), potassium, lithium, calcium and aluminium which advantageously allow for greater solubility or greater ease in formula-
5 tion and are considered the full equivalent of the free carboxylic acid. Also included within this class of functional derivatives are the hydroxamic acid derivatives which
10 are obtained by the condensation of an alkyl ester of the hereinabove described anilino nicotinic acids with hydroxylamine hydrochloride in the presence of sodium meth-
oxide.

15 The compositions described herein may be administered parenterally or enterally by incorporating them into dosage forms such as tablets, capsules, elixirs, solutions and sus-
20 pensions. Representative embodiments of the formulations containing the 2 - methyl - 3 - chloroanilino analogues of the compounds of this invention are disclosed in our copend-
ing Application No. 13779/68 (Serial No. 1147702). Similar formulations may be pre-
25 pared containing the compounds of this inven-
tion.

WHAT WE CLAIM IS:—

1. 2-Anilino-nicotinic acid compounds of the formula:



wherein M is hydrogen or lower alkyl; one of A and E is hydrogen and the other is chlorine or bromine; and D is chlorine or bromine or when A is chlorine and E is H
35 then D may also be methyl with an additional chlorine substituent at the 6-position of the phenyl ring.

2. Compounds as claimed in claim 1, wherein D is chloro, M is hydrogen, and A
40 and E have the same significance as indicated in claim 1.

3. Compounds as claimed in claim 1, wherein A is hydrogen, D and E are chloro, and M has the same significance as in
45 claim 1.

4. 2-(2,3-Dichloroanilino)-nicotinic acid.

5. 2-(3,5-Dichloroanilino)-nicotinic acid.

6. 2 - (2,6 - Dichloro - 3 - methylanilino) -
50 nicotinic acid.

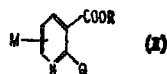
7. Pharmaceutically acceptable salts, esters and hydroxamic acid derivatives of the com-
pounds claimed in claims 1 to 6.

8. A salt as claimed in claim 7 which is an alkali metal salt.

9. A salt as claimed in claim 7 which is a diethanolamine salt.

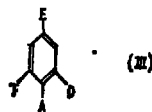
10. Process for the production of a com-

pound claimed in claim 1 characterised in that a compound of the general formula:



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is condensed with a compound of the general formula:



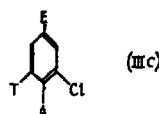
in which formulae R is a hydrogen atom or a substituent which does not interfere with the desired reaction, A, D, E and M are as defined in any of claims 1 to 8, one of Q and T is an unsubstituted or benzyl-, alkyl- or acyl-monosubstituted amino group and the other is a group capable of reacting with the amino group with the elimination of hydrogen therefrom to form the nitrogen bridge between the phenyl moiety and the pyridine moiety of the compounds of formula (I).
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11. Process as claimed in claim 10, wherein the symbol Q in the general formula (II) represents a halogen atom, an alkoxy, alkylthio, alkoxysulfonyl or nitro group, and the symbol T in the general formula (III) represents an unsubstituted or benzyl-, alkyl-, or acyl-monosubstituted amino group.

12. Process as claimed in claim 10, wherein the symbol Q in the general formula (II) represents an unsubstituted or monosubstituted amino group and the symbol T in the general formula (III) represents a halogen atom.

13. Process as claimed in any of claims 10 to 12 wherein R represents a hydrogen atom or an ester group or a potassium atom.

14. Process as claimed in any one of claims 10 to 13, wherein the compounds of the general formula (II) in which M is a hydrogen atom, Q is a halogen atom, an alkoxy, alkylthio, alkoxysulfonyl or nitro group, and R is a hydrogen atom or an ester group, are reacted with compounds of the general formula
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wherein A and E have the same significance as in claim 1, and T is an amino group
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- or a benzyl-, alkyl-, or acyl monosubstituted amino group.
15. Process as claimed in claim 14, wherein in the formula (IIIC), A represents a hydrogen atom and E represents a chloro atom.
16. Process as claimed in any one of claims 10 to 15, wherein the reaction is effected by heating the reactants in a high boiling inert solvent.
17. Process as claimed in any one of claims 10 to 15, wherein the reaction is effected by melting the reactants together.
18. Process as claimed in any one of claims 10 to 17 wherein potassium 2-chloronicotinate is reacted with 2,3-dichloroaniline.
19. Process as claimed in any one of claims 10 to 18, wherein the reaction is performed in the presence of copper powder and/or alkali metal carbonate.
20. Process as claimed in any one of claims 10 to 19 wherein the 2 - anilino - nicotinic acid compound resulting from the condensation is subjected to one or both of the following reaction steps to produce the desired compound:
- (i) removal of any substituent attached to the nitrogen atom; and
 - (ii) transformation of the compound in the form of the free acid into an ester, a pharmaceutically acceptable salt or a hydroxamic acid derivative.
21. Process as claimed in claim 20, wherein reaction step (i) is effected by a catalytic reduction procedure.
22. Process for the production of a compound claimed in any of claims 1 to 9, substantially as hereinbefore described.
23. A 2-anilino-nicotinic acid compound whenever obtained by a process as claimed in any one of claims 10 to 22.
24. A pharmaceutical composition which comprises, in association with a carrier compatible therewith, one or more of the 2-anilino-nicotinic acid compounds, claimed in any one of claims 1—9 or 23.
25. A pharmaceutical composition as claimed in claim 24, in which there is also present another active compound having anti-inflammatory properties.
26. A pharmaceutical composition as claimed in claim 25, in which the other active compound is phenylbutazone, acetylsalicylic acid or a steroid such as betamethasone.
27. Process for the preparation of a pharmaceutical composition as claimed in any one of claims 24 to 26, which comprises admixing a compound claimed in any one of claims 1—9, or 23 with a carrier and, optionally, another active compound having anti-inflammatory properties.

MATHYS & SQUIRE,
Chartered Patent Agents,
10, Fleet Street,
London, E.C.4.

Agents for the Applicants.

Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to patent No. 1,064,259.

