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(54) GLYCERYL ESTERS AND THEIR ANALGESIC ANTI-INFLAMMATORY USE

(71) 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 novel derivatives of 2-anilinonicotinic acid and of N-phenyl-anthranilic acid having valuable pharmacological properties, in particular anti-inflammatory properties, to processes for their preparation, and to pharmaceutical compositions containing them.

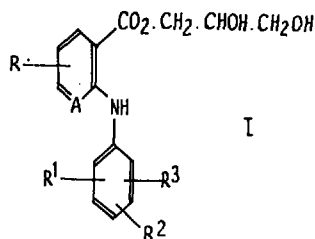
Anti-inflammatory agents which induce a minimum of undesirable side effects have been sought for a long time. Steroids having cortisone-like activity have been used to treat inflammation, but such steroids tend to induce undesirable side effects such as electrolyte imbalance and water retention. Derivatives of 2-anilinonicotinic acid and of N-phenyl-anthranilic acid have been found to be effective anti-inflammatory agents which are substantially free from the side effects due to steroids; these acids also have antipyretic and analgesic effects. However, these derivatives of 2-anilinonicotinic acid and of N-phenyl-anthranilic acid unfortunately possess other side effects; for example, they have a tendency to induce ulceration of the gastro-intestinal tract on oral administration. Thus, although use of the 2-anilinonicotinic acids and N-phenyl-anthranilic acids provides an improvement over steroid therapy, the acids themselves do possess some undesirable attributes. The usual salts and esters were found to offer substantially no improvement over the free

acids, and indeed were often less potent than the free acids in their anti-inflammatory, antipyretic and analgesic effects.

We have now found that the α -glyceryl esters of 2-anilinonicotinic acids and N-phenyl-anthranilic acids having anti-inflammatory antipyretic and analgesic effects are in general better tolerated in the gastro-intestinal tract than the free acids themselves. Although these glyceryl esters may be less potent in their anti-inflammatory, antipyretic and analgesic effects than the free acids, any loss in pharmacological properties is generally more than compensated by the increased tolerance of the gastro-intestinal tract towards the α -glyceryl esters.

Moreover, we have found that cyclic acetals and ketals of the aforesaid α -glyceryl esters, while useful primarily as intermediates in the preparation of the α -glyceryl esters themselves, also have valuable pharmacological properties.

According to the invention, therefore, we provide compounds of the formula



in which

- A represents a nitrogen atom or a CH group;
 R represents a hydrogen atom or a methyl group;

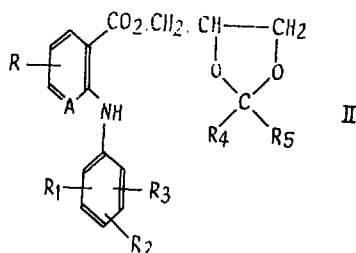
[Price 5s. 0d. (25p)]

- R^1 represents an alkyl, alkoxy, nitro, or trifluoromethyl group, or a halogen atom;
 R^2 represents an alkyl, nitro, or trifluoromethyl group, or a hydrogen or halogen atom;
 R^3 represents an alkyl, nitro, or trifluoromethyl group, or a hydrogen or halogen atom;

- and the pharmaceutically acceptable cyclic acetals and ketals thereof;
 and pharmaceutically acceptable salts of the compounds of the formula I and their pharmaceutically acceptable cyclic acetals and ketals.

- Preferred pharmaceutically acceptable salts of the compounds of the formula I and of their pharmaceutically acceptable cyclic acetals and ketals include those formed with maleic, salicylic, succinic, methylsulfonic, tartaric, citric, hydrochloric, hydrobromic, sulfuric, and phosphoric acid.

Preferred cyclic acetals and ketals include those of the formula



- in which A, R, R^1 , R^2 , and R^3 are as hereinbefore defined, and R^4 and R^5 , which may be the same or different, represent hydrogen atoms or alkyl, aryl, or aralkyl groups, or together form a polymethylene group.

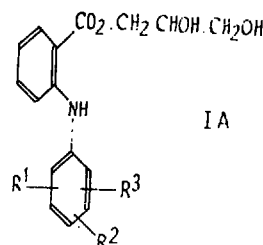
- When a cyclic acetal or ketal of a compound of the formula I is used therapeutically, a compound is preferably used in which R^4 represents a hydrogen atom or a lower alkyl group and R^5 represents a lower alkyl group, in particular a compound in which R^4 and R^5 are both methyl groups.

Throughout the specification and claims, the term "lower" as applied to alkoxy and alkyl groups indicates such groups having 1 to 4 carbon atoms.

- It will be observed that the β -carbon atom of the glyceryl moiety is asymmetrically substituted in the glyceryl esters themselves and in the cyclic acetals and ketals thereof, and that the compounds according to the invention therefore exist in stereoisomeric forms. All stereoisomeric forms, whether pure, mixtures, or racemates, fall within the scope of the invention.

- The following formulae IA, IB and IC indicate preferred groups of compounds within formula I:

Compounds of the formula



IA

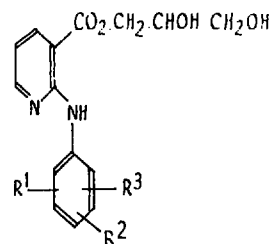
in which

- R^1 represents a lower alkyl, lower alkoxy, nitro, or trifluoromethyl group, or a halogen atom;

- R^2 represents a lower alkyl, nitro, or trifluoromethyl group, or a hydrogen or halogen atom; and

- R^3 represents a lower alkyl, nitro, or trifluoromethyl group, or a hydrogen or halogen atom;

Compounds of the formula



IB

in which

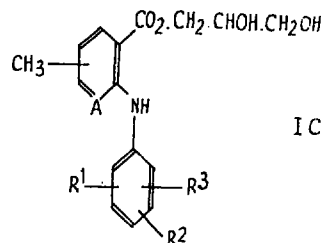
- R^1 represents a lower alkyl, lower alkoxy, nitro or trifluoromethyl group, or a halogen atom;

- R^2 represents a lower alkyl or trifluoromethyl group, or a hydrogen or halogen atom; and

- R^3 represents a lower alkyl or trifluoromethyl group, or a hydrogen or halogen atom;

and

Compounds of the formula



IC

- in which R^1 , R^2 , and R^3 are as defined for formula IA and A is nitrogen or the group CH.

The pharmaceutically acceptable cyclic acetals and ketals of the compounds of formulae IA, IB, and IC, together with the pharmaceutically acceptable acid addition

salts of these compounds and of their pharmaceutically acceptable cyclic acetals and ketals, are also preferred compounds.

Of the compounds within formula IA, those compounds in which not more than one of R^2 and R^3 represents a hydrogen atom are generally preferred. Of the compounds in which only one of R^2 and R^3 represents hydrogen, those are generally preferred in which R^1 and R^2 or R^3 substitute the 2- and 3-positions or the 3- and 5-positions. Of the compounds in which neither R^2 nor R^3 represents hydrogen, those are generally preferred in which R^1 , R^2 and R^3 substitute the 2-, 3- and 6-positions or the 3-, 5- and 6-positions.

A preferred group of compounds within formula IA comprises those compounds in which R^1 is lower alkyl, R^2 is hydrogen, and R^3 is halogen. A particularly preferred compound of this type on account of its especially favourable pharmacological properties is α -glyceryl N-(2-methyl-3-chlorophenyl)-anthranilate. Other particularly preferred compounds within formula IA on account of their especially favourable pharmacological properties are α -glyceryl N-(3-trifluoromethylphenyl)-anthranilate and α -glyceryl N-(2-methyl-3-nitrophenyl)-anthranilate.

Other preferred compounds within formula IA include those in the following Table:

Table 1

	glyceryl N-(2,3-dichlorophenyl)-anthranilate;
35	glyceryl N-(2,3-dimethylphenyl)-anthranilate;
	glyceryl N-(3-methyl-5-chlorophenyl)-anthranilate;
40	glyceryl N-(3-methyl-5-nitrophenyl)-anthranilate;
	glyceryl N-(3,5-dichlorophenyl)-anthranilate;
	glyceryl N-(2-methyl-3-chloro-6-nitrophenyl)-anthranilate;
45	glyceryl N-(2,3-dichloro-6-nitrophenyl)-anthranilate;
	glyceryl N-(2,3-dimethyl-6-nitrophenyl)-anthranilate;
	glyceryl N-(2-chloro-6-nitrophenyl)-anthranilate;
50	glyceryl N-(2,6-dimethyl-3-nitrophenyl)-anthranilate;
	glyceryl N-(2-nitro-3,6-dichlorophenyl)-anthranilate.
55	Of the compounds within formula IB, those compounds in which not more than one of R^2 and R^3 represents a hydrogen atom are generally preferred. Of the compounds in which only one of R^2 and R^3 represents hydrogen, those are generally preferred in which R^1 and R^2 or R^3 substitute the 2- and 3-positions, or the 3- and 5-positions, or the 2- and 6-positions. Of the compounds in which neither R^2 nor R^3 represents hydrogen, those
60	

are generally preferred in which R^1 , R^2 and R^3 substitute the 2-, 3- and 6-positions or the 3-, 5- and 6-positions.

A preferred group of compounds within formula IB comprises those compounds in which R^1 is nitro or halogen, R^2 is lower alkyl, and R^3 is hydrogen. Particularly preferred compounds of this type on account of their especially favourable pharmacological properties are α -glyceryl 2-(2-methyl-3-chloroanilino)-nicotinate, and α -glycerol 2-(2-methyl-nitroanilino)-nicotinate.

Other preferred compounds within formula IB include those in the following Table:

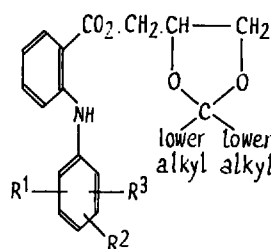
Table 2

glyceryl 2-(3-trifluoromethylanilino)-nicotinate;	80
glyceryl 2-(2,3-dichloroanilino)-nicotinate;	
glyceryl 2-(2,3-dimethylanilino)-nicotinate;	
glyceryl 2-(3-methyl-5-chloroanilino)-nicotinate;	85
glyceryl 2-(3-methyl-5-nitroanilino)-nicotinate;	
glyceryl 2-(3,5-dichloroanilino)-nicotinate;	
glyceryl 2-(2,6-dichloroanilino)-nicotinate;	
glyceryl 2-(2-methyl-3-chloro-6-nitroanilino)-nicotinate;	90
glyceryl 2-(2,3-dichloro-6-nitroanilino)-nicotinate;	
glyceryl 2-(2,3-dimethyl-6-nitroanilino)-nicotinate;	95
glyceryl 2-(3,5-dimethyl-6-nitroanilino)-nicotinate;	
glyceryl 2-(3,5-dichloro-6-nitroanilino)-nicotinate; and	
glyceryl 2-(2,6-dichloro-3-methylanilino)-nicotinate.	100

A preferred group of compounds within formula IC includes those compounds in which R^1 is nitro or halogen, R^2 is lower alkyl, and R^3 is hydrogen. Particularly preferred compounds of this type on account of their favourable pharmacological properties include:

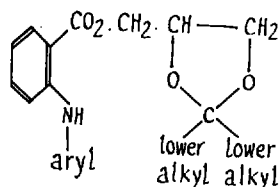
α -glyceryl 6-methyl-2-(2-methyl-3-chloroanilino)-nicotinate, and
 α -glyceryl 6-methyl-2-(2-methyl-3-nitroanilino)-nicotinate.

A preferred group of cyclic ketals of esters falling within formula IA comprises the compounds of the formula

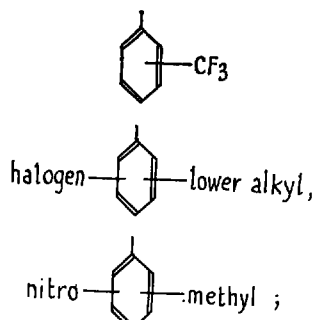


in which R^1 , R^2 and R^3 are as defined for

formula IA, more particularly the compounds of the formula



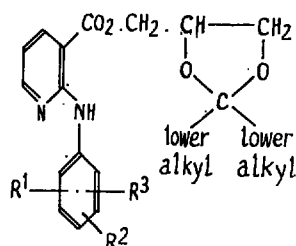
- 5 in which the group designated "aryl" has the formula:



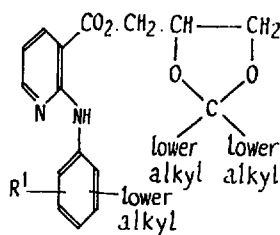
- 10 preferably all the lower alkyl groups are methyl groups. Particularly preferred compounds of this type, on the one hand owing to their use as intermediates and on the other hand owing to their favourable pharmacological properties, include

- 15 β,γ -isopropylidenedioxypropyl N-(3-trifluoromethylphenyl)-anthranilate;
 β,γ -isopropylidenedioxypropyl N-(2-methyl-3-chlorophenyl)-anthranilate; and
 20 β,γ -isopropylidenedioxypropyl N-(2-methyl-3-nitrophenyl)-anthranilate.

A preferred group of cyclic ketals of esters falling within formula IB comprises the compounds of the formula



- 25 in which R^1 , R^2 and R^3 are as defined for formula IB, more particularly the compounds of the formula

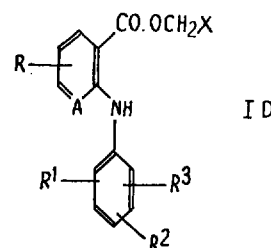


in which R^1 is nitro or halogen; preferably all the lower alkyl groups are methyl groups. Particularly preferred compounds of this type, on the one hand owing to their use as intermediates and on the other hand owing to their favourable pharmacological properties, include β,γ -isopropylidenedioxypropyl 2-(2-methyl-3-chloroanilino)-nicotinate, and β,γ -isopropylidenedioxypropyl 2-(2-methyl-3-nitroanilino)-nicotinate.

Particularly preferred cyclic ketals of the compounds of formula IC, on account of their use as intermediates and also on account of their favourable pharmacological properties, include

β,γ -isopropylidenedioxypropyl 6-methyl-2-(2-methyl-3-chloroanilino)-nicotinate, and β,γ -isopropylidenedioxypropyl 6-methyl-2-(2-methyl-3-nitroanilino)-nicotinate.

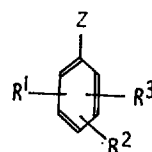
The compounds according to the invention can be prepared by known methods of condensation. Thus, for the preparation of a compound of the formula



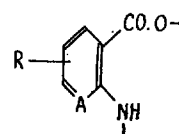
in which X represents an α,β -dihydroxy-ethyl group or a cyclic acetal or ketal thereof, and A, R, R^1 , R^2 and R^3 are as defined for formula I, a compound of the formula



can be condensed by known methods with a compound of the formula



in which R^1 , R^2 and R^3 are as defined for formula I, X^1 represents the group X hereinbefore defined or a vinyl or epoxyethyl group, Y and Z represent reactive groups capable of condensing during the reaction to leave the bridge

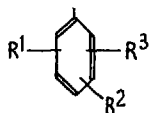


(in which R and A are as defined for formula I) between the groups



(in which X^1 is as hereinbefore defined) and

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(in which R^1 , R^2 and R^3 are as defined for formula I);

and, where X^1 represents a vinyl or epoxyethyl group, converting the product by known methods of oxidation and/or hydrolysis into a β,γ -dihydroxypropyl ester.

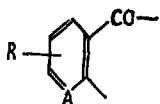
By the term "known methods" we mean those methods heretofore used or described in the chemical literature.

The oxidation and/or hydrolysis step to produce a β,γ -dihydroxypropyl ester can be effected in one or more stages. For example, when X^1 represents a vinyl group, the conversion of the immediate product into a β,γ -dihydroxypropyl ester can be effected in a single step oxidation with osmium tetroxide (substantially in the absence of other oxidising agents), or in more than one step by epoxidation of the double bond with an organic peracid and hydrolysis of the epoxide. Further reagents which may be used for the oxidation include potassium permanganate; silver chlorate and osmium tetroxide; hydrogen peroxide and osmium tetroxide; hydrogen peroxide and selenium dioxide; and silver iododibenzoate (followed by a hydrolysis step).

When X^1 represents an epoxyethyl group, the hydrolysis can be effected in one stage, but is generally more conveniently effected in two stages; for example, by opening the epoxide ring by reaction with an acid, e.g., *p*-nitrobenzoic acid, followed by hydrolysis.

It will be understood that the grouping

40



(in which R and A are as defined for formula I), will normally form a part of one of the reactive groups Y and Z and will therefore remain inert during the condensation, although reaction may take place at the free valencies thereof.

Suitable pairs of reactive groups Y and Z will be readily apparent to those skilled in the art, but some examples are indicated in the following discussion.

There is one ester bond and one imino bridge in the α -glyceryl esters of formula I and their cyclic ketals and acetals, and either the ester bond or the imino bridge may be formed in the condensation according to the

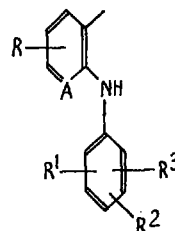
invention, the other having been formed previously.

When the ester bond is formed in the condensation according to the invention, it is preferred to react a compound of the formula



III A

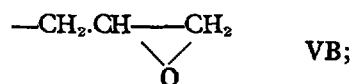
or an ester-forming derivative thereof, where P represents the grouping



in which A, R, R^1 , R^2 and R^3 are as defined for formula I, with a compound of the formula HO.Q , or an ester-forming derivative thereof; wherein Q represents one of the following groups:



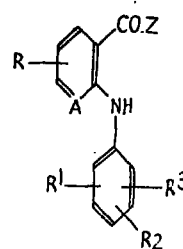
or a cyclic ketal or acetal thereof:



and thereafter, where Q represents formula VB or VC, the product is oxidised and/or hydrolysed as necessary, for example as hereinbefore described, to yield a β,γ -dihydroxypropyl ester.

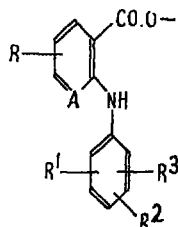
The following numbered paragraphs 1-6 disclose some preferred pairs of reactants:

1. A compound of the formula HO.Q (as defined above) can be conveniently reacted with an acid halide, preferably the chloride, or an anhydride, preferably with symmetrical anhydride or a mixed anhydride formed with a sterically hindered acid, such as pivalic acid, of a compound of the form III A. That is, a compound of the formula HO.Q is preferably reacted with a compound of the formula



90

in which A, R, R¹, R² and R³ are as defined for formula I and Z is a halogen atom or one of the groups



- 5 in which A, R, R¹, R² and R³ are as defined for formula I, and



The symmetrical anhydride of the compound of the formula IIIA can be prepared from the compound itself and a carbodi-imide, e.g., dicyclohexylcarbodi-imide. The anhydride is preferably reacted with the compound of the formula HO.Q at elevated temperature in the presence of a catalyst, e.g., zinc chloride, and in the presence of an inert organic solvent.

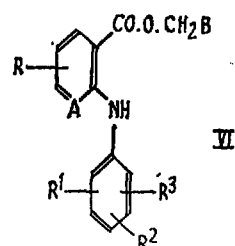
2. Alternatively, a compound of the formula HO.Q can be condensed in the presence of a dehydrating agent directly with a compound of the formula IIIA. Preferred dehydrating agents include carbodi-imides, especially dicyclohexylcarbodi-imide; α -alkynylamines are also useful as dehydrating agents. It should however be noted that many carbodi-imides react with the epoxy group of epoxypentyl alcohol, that glycerol itself is likely to form a cyclic adduct with many carbodi-imides, and that allyl alcohol can be converted into diallyl ether by means of carbodi-imides; therefore in this reaction, the preferred reactant of the formula IV is a cyclic ketal or acetal of glycerol.

3. In a modification of the process described in the preceding paragraph, the dehydrating agent — e.g., carbodi-imide or α -alkynylamine, preferably dicyclohexylcarbodi-imide — is reacted either with a compound of the formula IIIA or with a compound of the formula HO.Q, and the resulting product is reacted respectively with a compound of the formula HO.Q or with a compound of the formula IIIA. When the compound HO.Q is reacted with a dehydrating agent such as a carbodi-imide, HO.Q is preferably a cyclic acetal or ketal of glycerol, for the reasons set out in the preceding paragraph.

Reaction of the compound HO.Q with a carbodi-imide is normally effected in the presence of a catalyst, preferably a copper salt, e.g., cuprous or cupric chloride. The resulting addition product is then reacted with a compound of the formula IIIA in the presence of an inert organic solvent, e.g. dioxan, preferably at temperatures between room temperature and 150° C.

Reaction of a compound of the formula IIIA with a carbodi-imide is normally effected in a basic solvent, e.g. pyridine. The reaction product can be condensed with the compound of the formula HO.Q under transesterification conditions.

4. A particularly preferred method for the preparation of compounds of the formula I and cyclic acetals and ketals thereof comprises transesterification of a reactive ester of a compound of the formula IIIA with a compound of the formula HO.Q. The reactive ester preferably has the formula

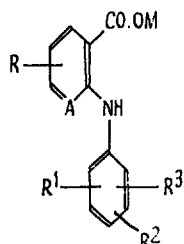


in which B represents a cyano, carbamoyl (e.g., N,N-dimethylcarbamoyl), alkoxycarbonyl (e.g., ethoxycarbonyl or methoxycarbonyl) or acyl (e.g., alkanoyl or aroyl, especially acetyl or benzoyl), and A, R, R¹, R², and R³ are as defined for formula I. This transesterification is preferably effected in the presence of a basic catalyst, e.g. anhydrous potassium carbonate. As solvent an excess of the compound of the formula HO.Q is conveniently used, since the transesterification is reversible. The reaction is conveniently effected at temperatures in the range of 80—250° C, for example at the reflux temperature of the reaction mixture.

The reactive ester is preferably prepared by reaction of a compound of the formula IIIA with a compound of the formula Cl.CH₂.B (where B is as hereinbefore defined) in the presence of a tertiary base, e.g., triethylamine. The preferred compound of the formula Cl.CH₂.B is chloroacetonitrile. Reactive esters which are particularly useful in the reaction described in the preceding numbered paragraph 4 are those in which the esterifying radical has an electron-withdrawing substituent on its α -carbon atom, e.g., a cyano or carbonyl group. Especially preferred esters are those of the formula VI hereinbefore defined; the reactive esters of choice are the cyano-methyl esters.

Another group of esters useful in the transesterification reaction of the preceding numbered paragraph 4 comprises esters in which the esterifying radical has its α -carbon atom doubly bonded to another carbon atom (e.g., the esters are enol esters, or esters formed by reaction of an α -alkynylamine with a compound of the formula IIIA) or to a nitrogen atom, in particular where the esters are the reaction product of a carbodi-imide (especially dicyclohexylcarbodi-imide) and a compound of the formula IIIA.

5. A compound of the formula

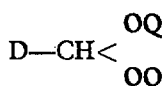


- 5 in which M represents one equivalent of a metal ion, preferably silver or an alkali metal e.g. sodium, and A, R, R¹, R², and R³ are as defined for formula I, can be reacted with a compound of the formula



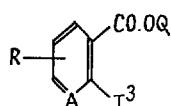
- 10 in which Q is as hereinbefore defined and W is a reactive ester residue, preferably a halogen atom or a sulphonate ester group.

6. A compound of the formula IIIA can be condensed with a compound of the formula

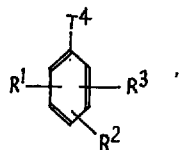


- 15 in which D represents a secondary amino group, for example a dimethylamino group, and Q is as hereinbefore defined.

- 20 When the imino bridge is formed in the condensation according to the invention, the process according to the invention comprises reacting a compound of the formula



with a compound of the formula



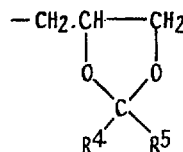
- 25 in which A, R, R¹, R² and R³ are as defined for formula I, Q is as hereinbefore defined, and one of T³ and T⁴ is an —NH₂ group and the other is a monovalent group which will condense with an —NH₂ group to form an imino bridge.

- 30 When T³ is an —NH₂ group, T⁴ must be a halogen atom, preferably a chlorine or bromine atom; when T⁴ is an —NH₂ group, T³ can be a halogen atom or other reactive residue, for example an alkoxy, alkylthio, alkoxy sulfonyl, or nitro group.

The reactants can be fused together, for example at 140—200° C, or can be heated in a high-boiling organic solvent, for example

cymene or xylene. The reaction may if desired be effected in the presence of a catalyst, preferably copper powder, and/or a base. The base can comprise one mole excess of the compound in which T³ or T⁴ represents —NH₂, or a tertiary organic base (which can also function as solvent), or an inorganic base, e.g., potassium carbonate.

In the foregoing processes, Q preferably represents a cyclic ketal or acetal of a group of the formula VA, more preferably a group of the formula



in which R⁴ and R⁵ are as hereinbefore defined. The preferred reactant of the formula HO.Q is 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolan.

When the product of the foregoing processes is an α-glyceryl ester and a cyclic ketal or acetal (dioxolan) thereof is required, the α-glyceryl ester can be reacted with the appropriate aldehyde or ketone in the presence of a condensing agent. Conversely, when the product of the said foregoing processes is a cyclic ketal or acetal (dioxolan) of the α-glyceryl ester and the α-glyceryl ester itself is required, the ketal or acetal group can be selectively removed by known methods. This removal can be effected by selectively hydrolysis, preferably under mildly acidic conditions, for example by means of aqueous acetic acid or p-toluene sulfonic acid hydrate in a low-boiling solvent such as tetrahydrofuran or dioxan; or by reaction of the dioxolan with boron trichloride at reduced temperature, preferably about —80° C, conveniently in the presence of an inert organic solvent such as methylene chloride, followed by hydrolysis of the resulting borate complex. Alternatively, certain dioxolans, notably those formed with aromatic aldehydes (R⁴=a hydrogen atom; R⁵=an aromatic group) can be cleaved to the α-glyceryl ester by hydrogenation, for example using palladium on charcoal or calcium carbonate as catalyst. Dioxolans formed with benzaldehyde (R⁴=H, R⁵=phenyl) are particularly preferred for hydrogenolysis.

Where a compound of the formula I hereinbefore defined or cyclic ketal or acetal thereof is required and the product is an acid addition salt thereof, the salt can be converted into the compound of formula I or ketal or acetal thereof by reaction with a base. Alternatively, where the product is a compound of the formula I hereinbefore defined or cyclic acetal or ketal thereof, and a pharmaceutically acceptable acid addition salt thereof is re-

quired. the compound of the formula I or acetal or ketal thereof can be converted into a pharmaceutically acceptable acid addition salt, for example by reaction with an acid or functional derivative thereof, preferably with maleic, salicylic, succinic, methylsulfonic, tartaric, citric, hydrochloric, hydrobromic, sulfuric, or phosphoric acid.

When a glyceryl ester or cyclic acetal or ketal thereof having a particular stereochemistry in the glyceryl moiety is required, it is normally preferred to esterify the acid of the formula IIIA or reactive derivative thereof with a resolved enantiomer of a cyclic ketal or acetal or glycerol.

The following examples illustrate the preparation of compounds according to the invention:

EXAMPLE 1.

20 A: Preparation of Reactive Esters of the N-phenyl-anthranilic acids

Cyanomethyl N (3-trifluoromethylphenyl)-anthranilate

A mixture of 15 g. of N-(3-trifluoromethylphenyl)-anthranilic acid, 45 ml. of triethylamine and 9 ml. of chloroacetonitrile is stirred and heated on a steam bath for one and a quarter hours. The resulting reaction mixture is poured into water and the product filtered off. The so-obtained colorless product melts at 116—117° C after recrystallization from isopropyl ether.

In a similar manner by substituting the N-3-trifluoromethylphenyl reactant of this example with equivalent quantities of N-(2-methyl-3-chlorophenyl)-anthranilic acid; N-(2-methyl-3-nitrophenyl)-anthranilic acid; N-(2-methyl-3-chloro-6-nitrophenyl)-anthranilic acid; N-(2-chloro-6-nitrophenyl)-anthranilic acid; N-(2,3-dimethylphenyl)-anthranilic acid; N-(2,3-dichlorophenyl)-anthranilic acid; N-(2,3-dibromophenyl)-anthranilic acid; N-(2,6-dimethyl-3-nitrophenyl)-anthranilic acid; N-(2,3-dichloro-6-methylphenyl)-anthranilic acid; N-(2,3-dichloro-6-nitrophenyl)-anthranilic acid; N-(3-methyl-5,6-dichlorophenyl)-anthranilic acid; N-(3-methyl-5-chlorophenyl)-anthranilic acid; N-(3-methyl-5-bromophenyl)-anthranilic acid; N-(3-methyl-5-nitrophenyl)-anthranilic acid; N-(3,5-dichlorophenyl)-anthranilic acid; N-(3,5-dimethylphenyl)-anthranilic acid; N-(2-methyl-3-trifluoromethylphenyl)-anthranilic acid; and N-(2,6-dichloro-3-methylphenyl)-anthranilic acid, and by substantially following the procedures set forth in this example, there are produced cyanomethyl N-(2-methyl-3-chlorophenyl)-anthranilate; cyanomethyl N-(2-methyl-3-nitrophenyl)-anthranilate; cyanomethyl N-

(2-methyl-3-chloro-6-nitrophenyl)-anthranilate; cyanomethyl N-(2-chloro-6-nitrophenyl)-anthranilate; cyanomethyl N-(2,3-dimethylphenyl)-anthranilate; cyanomethyl N-(2,3-dichlorophenyl)-anthranilate; cyanomethyl N-(2,3-dibromophenyl)-anthranilate; cyanomethyl N-(2,6-dimethyl-3-nitrophenyl)-anthranilate; cyanomethyl N-(2,3-dichloro-6-methylphenyl)-anthranilate; cyanomethyl N-(2,3-dichloro-6-nitrophenyl)-anthranilate; cyanomethyl N-(3-methyl-5,6-dichlorophenyl)-anthranilate; cyanomethyl N-(3-methyl-5-chlorophenyl)-anthranilate; cyanomethyl N-(3-methyl-5-bromophenyl)-anthranilate; cyanomethyl N-(3-methyl-5-nitrophenyl)-anthranilate; cyanomethyl N-(3,5-dichlorophenyl)-anthranilate; cyanomethyl N-(3,5-dimethylphenyl)-anthranilate; cyanomethyl N-(2-methyl-3-trifluoromethylphenyl)-anthranilate; cyanomethyl N-(2,6-dichlorophenyl)-anthranilate; and cyanomethyl N-(2,6-dichloro-3-methylphenyl)-anthranilate, respectively.

B: Ester Interchange Reaction

β,γ-Isopropylidenedioxypropyl N-(3-trifluoromethylphenyl)-anthranilate

A mixture of 11 g. of cyanomethyl N-(3-trifluoromethylphenyl)-anthranilate, 32 g. of 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolan and 600 mg. of anhydrous potassium carbonate is heated on a steam bath for one hour. The resulting reaction mixture is poured into 500 ml. of water, extracted with ether and the ether layer washed with water several times. The ether extract is dried and concentrated leaving the product as a pale yellow oil.

Similarly, by replacing the cyanomethyl N-(3-trifluoromethyl)-anthranilate with equivalent quantities of those esters following step A of this Example, and by substantially following the procedure of step B of this example, there are produced β,γ-isopropylidenedioxypropyl N-(2-methyl-3-chlorophenyl)-anthranilate; β,γ-isopropylidenedioxypropyl N-(2-methyl-3-nitrophenyl)-anthranilate; β,γ-isopropylidenedioxypropyl N-(2-methyl-3-chloro-6-nitrophenyl)-anthranilate; β,γ-isopropylidenedioxypropyl N-(2-chloro-6-nitrophenyl)-anthranilate; β,γ-isopropylidenedioxypropyl N-(2,3-dimethylphenyl)-anthranilate; β,γ-isopropylidenedioxypropyl N-(2,3-dichlorophenyl)-anthranilate; β,γ-isopropylidenedioxypropyl N-(2,3-dibromophenyl)-anthranilate; β,γ-isopropylidenedioxypropyl N-(2,6-dimethyl-3-nitrophenyl)-anthranilate; β,γ-isopropylidenedioxypropyl N-(2,3-dichloro-6-methylphenyl)-anthranilate; β,γ-isopropylidenedioxypropyl N-(2,3-dichloro-6-nitrophenyl)-anthranilate; β,γ-isopropylidenedioxypropyl N-(3-methyl-5,6-di-

- chlorophenyl) - anthranilate; β,γ - isopropylidenedioxypropyl N - (3 - methyl - 5 - chlorophenyl) - anthranilate; β,γ - isopropylidenedioxypropyl N - (3 - methyl - 5 - bromophenyl) - anthranilate; β,γ - isopropylidenedioxypropyl N - (3 - methyl - 5 - nitrophenyl) - anthranilate; β,γ - isopropylidenedioxypropyl N - (3,5 - dichlorophenyl) - anthranilate; β,γ - isopropylidenedioxypropyl N - (3,5 - dimethylphenyl) - anthranilate; β,γ - isopropylidenedioxypropyl N - (2 - methyl - 3 - trifluoromethylphenyl) - anthranilate; β,γ - isopropylidenedioxypropyl N - (2,6 - dichlorophenyl) - anthranilate; and β,γ - isopropylidenedioxypropyl N - (2,6 - dichloro - 3 - methylphenyl) - anthranilate, respectively.

C: Preparation of Glyceryl Esters

Glyceryl-N-(3-trifluoromethylphenyl)-anthranilate

- 20 A solution of 12.6 g. of β,γ -isopropylidenedioxypropyl N - (3 - trifluoromethylphenyl)-anthranilate and 90 ml. of 75% acetic acid is heated for 30 minutes on a steam bath. The solution is poured on to ice, neutralized with
25 cold dilute sodium hydroxide solution, extracted with ether and the ether layer separated, dried and concentrated. Recrystallization from benzene-hexane yields the product as a colorless solid, m.p. 94—95° C.
- 30 In a similar manner, by substituting β,γ -isopropylidenedioxypropyl N - (3 - trifluoromethylphenyl) - anthranilate with equivalent quantities of those β,γ - isopropylidenedioxypropyl esters following step B of the example,
35 and by substantially following the procedure of step C of this example, there are produced glyceryl - N - (2 - methyl - 3 - chlorophenyl)-anthranilate; glyceryl - N - (2 - methyl - 3 - nitrophenyl) - anthranilate; glyceryl - N - (2 - methyl - 3 - chloro - 6 - nitrophenyl) - anthranilate; glyceryl - N - (2 - chloro - 6 - nitrophenyl) - anthranilate; glyceryl - N - (2,3 - dimethylphenyl) - anthranilate; glyceryl - N - (2,3 - dichlorophenyl) - anthranilate; glyceryl - N - (2,3 - dibromophenyl) - anthranilate;
45 glyceryl - N - (2,6 - dimethyl - 3 - nitrophenyl) - anthranilate; glyceryl - N - (2,3 - dichloro - 6 - methylphenyl) - anthranilate; glyceryl - N - (2,3 - dichloro - 6 - nitrophenyl) - anthranilate; glyceryl - N - (3 - methyl - 5,6 - dichlorophenyl) - anthranilate; glyceryl - N - (3 - methyl - 5 - chlorophenyl)-anthranilate; glyceryl - N - (3 - methyl - 5 - bromophenyl) - anthranilate; glyceryl - N - (3 - methyl - 5 - nitrophenyl) - anthranilate;
55 glyceryl - N - (3,5 - dichlorophenyl) - anthranilate; glyceryl - N - (3,5 - dimethylphenyl)-anthranilate; glyceryl - N - (2 - methyl - 3 - trifluoromethylphenyl) - anthranilate; glyceryl - N - (2,6 - dichlorophenyl) - anthranilate, and glyceryl - N - (2,6 - dichloro - 3 - methylphenyl) - anthranilate, respectively.

EXAMPLE 2.

A: Preparation of Anilonic Nicotinic Acids

2-(2-Methyl-3-chloroanilino)-nicotinic acid 65

Mix 15.7 g. (0.1 mole) of 2-chloronicotinic acid with 28.2 g. (0.2 mole) of 2-methyl-3-chloroaniline. 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. 233—235° C. 75

Alternatively, the compound of step A of this Example, 2-(2-methyl-3-chloroanilino)-nicotinic acid, may be prepared by heating together 30 g. of ethyl 2-chloronicotinate and 45.6 g. of 2-methyl-3-chloroaniline at 200° C for 10 minutes. Cool, dissolve the residue in 100 ml. hot ethanol, cool and filter obtaining the ethyl ester of the compound of step A of this example, m.p. 77.5—79° C. 80

Dissolve 30.8 g. of the ethyl ester in a solution of 13.25 g. of potassium hydroxide in 1 liter 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 step A of this example. 85

Similarly by substituting the aniline reactant of step A of this example with equivalent quantities of 2 - methyl - 3 - trifluoromethylaniline; 2-methyl-3-bromoaniline; 2-methoxy-3-chloroaniline; 2-chloro-3-nitroaniline; 2,3-dichloroaniline; 2,3-dibromoaniline; 2,3-ditrifluoromethylaniline; 2,3-dimethylaniline; 3-methyl - 5 - chloroaniline; 3 - methyl - 5-nitroaniline; 3-methyl-5-bromoaniline; 3-trifluoromethylaniline; 3 - methyl - 5 - trifluoromethylaniline; 3,5-dimethylaniline; 3-methoxy-5-chloroaniline; 3-chloro-5-nitroaniline; 3,5-dichloroaniline; 3,5-dibromoaniline; 3,5-ditrifluoromethylaniline; 2,6-dimethylaniline; 2-methyl-3-nitroaniline; 2-methyl-3-chloro-6-nitroaniline; 2-chloro-3-methylaniline; 2-methyl-3-nitro-6-chloroaniline; 2,3-dichloro-6-nitroaniline; 2,3-dimethyl-6-nitroaniline; 2-chloro-6-nitroaniline; 2-methyl-6-nitroaniline; 2-ethyl-6-nitroaniline; 2,6-dichloroaniline; 3,5-dimethyl-6-nitroaniline; 3,5-dichloro-6-nitroaniline; and 2,6-dichloro-3-methylaniline, and by substantially following the procedures outlined therein, there are produced 2-(2-methyl-3 - trifluoromethylanilino) - nicotinic acid; 2-(2 - methyl - 3 - bromoanilino) - nicotinic acid; 2 - (2 - methoxy - 3 - chloroanilino) - nicotinic acid; 2-(2-chloro-3-nitroanilino)-nicotinic acid; 2 - (2,3 - dichloroanilino) - nicotinic acid; 2 - (2,3 - dibromoanilino) - nicotinic acid; 2 - (2,3 - di - trifluoromethylanilino) - nicotinic acid; 2 - (2,3 - dimethylanilino) - nicotinic acid; 2 - (3 - methyl - 5 - chloroanilino) - nicotinic acid; 2 - (3 - methyl - 5 - nitroanilino)- 125

- nicotinic acid; 2 - (3 - methyl - 5 - bromo-anilino) - nicotinic acid; 2 - (3 - trifluoromethylanilino) - nicotinic acid; 2 - (3 - methyl - 5 - trifluoromethylanilino) - nicotinic acid; 5
2 - (3,5 - dimethylanilino) - nicotinic acid; 2 - (3 - methoxy - 5 - chloroanilino) - nicotinic acid; 2 - (3 - chloro - 5 - nitroanilino) - nicotinic acid; 2 - (3,5 - dichloroanilino) - nicotinic acid; 2 - (3,5 - dibromoanilino) - nicotinic acid; 10
2 - (3,5 - di - trifluoromethylanilino) - nicotinic acid; 2 - (2,6 - dimethylanilino) - nicotinic acid; 2 - (2 - methyl - 3 - nitroanilino) - nicotinic acid; 2 - (2 - methyl - 3 - chloro - 6 - nitroanilino) - nicotinic acid; 15
2 - (2 - chloro - 3 - methylanilino) - nicotinic acid; 2 - (2 - methyl - 3 - nitro - 6 - chloroanilino) - nicotinic acid; 2 - (2,3 - dichloro - 6 - nitroanilino) - nicotinic acid; 2 - (2,3 - dimethyl - 6 - nitroanilino) - nicotinic acid; 20
2 - (2 - chloro - 6 - nitroanilino) - nicotinic acid; 2 - (2 - methyl - 6 - nitroanilino) - nicotinic acid; 2 - (2 - ethyl - 6 - nitroanilino) - nicotinic acid; 2 - (2,6 - di - chloroanilino) - nicotinic acid; 2 - (3,5 - dimethyl - 6 - nitroanilino) - nicotinic acid; 25
2 - (3,5 - dichloro - 6 - nitroanilino) - nicotinic acid; and 2 - (2,6 - dichloro - 3 - methylanilino) - nicotinic acid, respectively.

B: Preparation of Reactive Ester Intermediates

30 Cyanomethyl 2-(2-methyl-3-chloroanilino)-nicotinate

A mixture of 30 g. of 2-(2-methyl-3-chloroanilino)-nicotinic acid, 12.6 g. of chloroacetonitrile, and 16.8 g. of triethylamine is stirred and heated at reflux temperature for four hours. The reaction mixture is poured into water and the product is filtered off to yield cyanomethyl 2-(2-methyl-3-chloroanilino)-nicotinate, m.p. 137°—138° C.

- Similarly by substituting the 2-(2-methyl-3-chloroanilino)-nicotinic acid reactant of step B of this example with equivalent quantities of those 2-anilino-nicotinic acids illustrated in step A of this example, and by substantially following the procedure of step B of this example, there are produced cyanomethyl - 2 - (2-methyl - 3 - trifluoromethylanilino) - nicotinate; cyanomethyl - 2 - (2 - methyl - 3 - bromoanilino) - nicotinate; cyanomethyl - 2 - (2 - methoxy - 3 - chloroanilino) - nicotinate; 50
cyanomethyl - 2 - (2 - chloro - 3 - nitroanilino) - nicotinate; cyanomethyl - 2 - (2,3 - dichloroanilino) - nicotinate; cyanomethyl - 2 - (2,3 - dibromoanilino) - nicotinate; cyanomethyl - 2 - (2,3 - di - trifluoromethylanilino) - nicotinate; cyanomethyl - 2 - (2,3 - dimethylanilino) - nicotinate; cyanomethyl - 2 - (3-methyl - 5 - chloroanilino) - nicotinate; cyanomethyl - 2 - (3 - methyl - 5 - nitroanilino) - nicotinate; cyanomethyl - 2 - (3 - methyl - 5 - bromoanilino) - nicotinate; cyanomethyl - 2 - (3 - trifluoromethylanilino) - nicotinate; cyano- 60
methyl - 2 - (3 - methyl - 5 - trifluoromethyl-

anilino) - nicotinate; cyanomethyl - 2 - (3,5-dimethylanilino) nicotinate; cyanomethyl - 2 - (3 - methoxy - 5 - chloroanilino) - nicotinate; 65
cyanomethyl - 2 - (3 - chloro - 5 - nitroanilino) - nicotinate; cyanomethyl - 2 - (3,5 - dichloroanilino) - nicotinate; cyanomethyl - 2 - (3,5 - dibromoanilino) - nicotinate; cyanomethyl - 2 - (3,5 - di - trifluoromethylanilino) - nicotinate; cyanomethyl - 2 - (2,6 - dimethylanilino) - nicotinate; cyanomethyl - 2 - (2-methyl - 3 - nitroanilino) - nicotinate; cyano- 70
methyl - 2 - (2 - methyl - 3 - chloro - 6 - nitroanilino) - nicotinate; cyanomethyl - 2 - (2 - chloro - 3 - methylanilino) - nicotinate; cyanomethyl - 2 - (2 - methyl - 3 - nitro - 6 - chloroanilino) - nicotinate; cyanomethyl - 2 - (2,3 - dichloro - 6 - nitroanilino) - nicotinate; cyanomethyl - 2 - (2,3 - dimethyl - 6 - nitroanilino) - nicotinate; cyanomethyl - 2 - (2 - chloro - 6 - nitroanilino) - nicotinate; cyano- 75
methyl - 2 - (2 - methyl - 6 - nitroanilino) - nicotinate; cyanomethyl - 2 - (2 - ethyl - 6 - nitroanilino) - nicotinate; cyanomethyl - 2 - (2,6 - dichloroanilino) - nicotinate; cyano- 80
methyl - 2 - (3,5 - dimethyl - 6 - nitroanilino) - nicotinate; cyanomethyl - 2 - (3,5 - dichloro - 6 - nitroanilino) - nicotinate; cyanomethyl - 2 - (2,6 - dichloro - 3 - methylanilino) - nicotinate, 90
respectively.

Alternatively, by substituting the chloroacetonitrile reactant with equivalent quantities of chloroacetone, chloracetamide, phenacylchloride, and ethylchloroacetate, and by substantially following the procedure of step B of this example, the following compounds are produced from the first four anilino-nicotinic acids listed at the end of step A of this Example: acetonyl 2 - (2 - methyl - 3 - chloroanilino) - nicotinate; carbamoylmethyl 2 - (2-methyl - 3 - trifluoromethylanilino) - nicotinate; phenacyl 2 - (2 - methyl - 3 - bromoanilino) - nicotinate; and ethoxycarbonylmethyl 2 - (2 - methoxy - 3 - chloroanilino) - 105
nicotinate, respectively.

C: Preparation of Cyclic Acetal Intermediates

β,γ -Isopropylidenedioxypopyl 2-(2-methyl-3-chloroanilino)-nicotinate

A mixture of 6 g. of cyanomethyl 2-(2-methyl-3-chloroanilino)-nicotinate, 18 g. of 2,2 - dimethyl - 4 - hydroxymethyl - 1,3-dioxolan and 300 mg. of anhydrous potassium carbonate is stirred and heated on a steam bath for one and a half hours. The resulting mixture is treated with water, cooled and filtered to yield β,γ -isopropylidenedioxypopyl 2-(2-methyl-3-chloroanilino)-nicotinate, m.p. 98°—100° C.

Similarly by substituting the cyanomethyl 2 - (2 - methyl - 3 - chloroanilino) - nicotinate with equivalent quantities of those cyanomethyl anilino-nicotinates exemplified in step B of this example, and by substantially following the

- procedure outlined in step C of this example, there are produced β,γ - isopropylidenedioxypropyl 2 - (2 - methyl - 3 - trifluoromethylanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (2 - methyl - 3 - bromoanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (2 - methoxy - 3 - chloroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (2 - chloro - 3 - nitroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (2,3 - dichloroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (2,3 - dibromoanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (2,3 - di-trifluoromethylanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (2,3 - dimethylanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (3 - methyl - 5 - chloroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (3 - methyl - 5 - nitroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (3 - methyl - 5 - bromoanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (3 - trifluoromethylanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (3 - methyl - 5 - trifluoromethylanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (3,5 - dimethylanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (3 - methoxy - 5 - chloroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (3 - chloro - 5 - nitroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (3,5 - dichloroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (3,5 - dibromoanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (3,5 - di-trifluoromethylanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (2,6 - dimethylanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (2 - methyl - 3 - nitroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (2 - methyl - 3 - chloro - 6 - nitroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (2 - chloro - 3 - methylanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (2 - methyl - 3 - nitro - 6 - chloroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (2,3 - dichloro - 6 - nitroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl 2 - (2,3 - dimethyl - 6 - nitroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl - 2 - (2 - chloro - 6 - nitroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl - 2 - (2 - methyl - 6 - nitroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl - 2 - (2 - ethyl - 6 - nitroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl - 2 - (2,6 - dichloroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl - 2 - (3,5 - dimethyl - 6 - nitroanilino) - nicotinate; β,γ - isopropylidenedioxypropyl - 2 - (3,5 - dichloro - 6 - nitroanilino) - nicotinate; and β,γ - isopropylidenedioxypropyl - 2 - (2,6 - dichloro - 3 - methylanilino) - nicotinate, respectively.

D: Preparation of Glyceryl Ester Final Products

Glyceryl 2-(2-methyl-3-chloroanilino)-nicotinate 65

A mixture of 6.1 g. of β,γ -isopropylidenedioxypropyl 2 - (2 - methyl - 3 - chloroanilino) - nicotinate and 60 ml. of 0.5N hydrochloric acid is heated at 55–60° C for one hour. The resulting solution is poured on to ice and neutralized, and the product is filtered off and recrystallized from benzene to yield glyceryl 2 - (2 - methyl - 3 - chloroanilino) - nicotinate, m.p. 113°–114° C. 70 75

Similarly, by substituting those β,γ -isopropylidenedioxypropyl - anilonic nitrates listed in step C of this example and by hydrolysing said esters substantially according to the procedure of step D of this example, there are produced glyceryl 2-(2-methyl-3-trifluoromethylanilino) - nicotinate; glyceryl 2-(2 - methyl - 3 - bromoanilino) - nicotinate; glyceryl 2 - (2 - methoxy - 3 - chloroanilino) - nicotinate; glyceryl 2 - (2 - chloro - 3 - nitroanilino) - nicotinate; glyceryl 2 - (2,3 - dichloroanilino) - nicotinate; glyceryl 2 - (2,3 - dibromoanilino) - nicotinate; glyceryl 2 - (2,3 - di-trifluoromethylanilino) - nicotinate; glyceryl 2 - (2,3 - dimethylanilino) - nicotinate; glyceryl 2 - (3 - methyl - 5 - chloroanilino) - nicotinate; glyceryl 2 - (3 - methyl - 5 - nitroanilino) - nicotinate; glyceryl 2 - (3 - methyl - 5 - bromoanilino) - nicotinate; glyceryl 2 - (3 - trifluoromethylanilino) - nicotinate; glyceryl 2 - (3 - methyl - 5 - trifluoromethylanilino) - nicotinate; glyceryl 2 - (3,5 - dimethylanilino) - nicotinate; glyceryl 2 - (3 - methoxy - 5 - chloroanilino) - nicotinate; glyceryl 2 - (3 - chloro - 5 - nitroanilino) - nicotinate; glyceryl 2 - (3,5 - dichloroanilino) - nicotinate; glyceryl 2 - (3,5 - dibromoanilino) - nicotinate; glyceryl 2 - (3,5 - di-trifluoromethylanilino) - nicotinate; glyceryl 2 - (2,6 - dimethylanilino) - nicotinate; glyceryl 2 - (2 - methyl - 3 - nitroanilino) - nicotinate; glyceryl 2 - (2 - methyl - 3 - chloro - 6 - nitroanilino) - nicotinate; glyceryl 2 - (2 - chloro - 3 - methylanilino) - nicotinate; glyceryl 2 - (2 - methyl - 3 - nitro - 6 - chloroanilino) - nicotinate; glyceryl 2 - (2,3 - dichloro - 6 - nitroanilino) - nicotinate; glyceryl 2 - (2,3 - dimethyl - 6 - nitroanilino) - nicotinate; glyceryl 2 - (2 - chloro - 6 - nitroanilino) - nicotinate; glyceryl 2 - (2 - methyl - 6 - nitroanilino) - nicotinate; glyceryl 2 - (2 - ethyl - 6 - nitroanilino) - nicotinate; glyceryl 2 - (2,6 - dichloroanilino) - nicotinate; glyceryl 2 - (3,5 - dimethyl - 6 - nitroanilino) - nicotinate; glyceryl 2 - (3,5 - dichloro - 6 - nitroanilino) - nicotinate; and glyceryl 2 - (2,6 - dichloro - 3 - methylanilino) - nicotinate, respectively. 80 85 90 95 100 105 110 115 120

EXAMPLE 3.

A: Ethyl 6-methyl-2-(2-methyl-3-chloroanilino)-nicotinate

5 A mixture of 10.2 g. of ethyl 2-chloro-6-methyl-nicotinate and 14.5 g. of 2-methyl-3-chloroaniline was heated at 200—220° C for 10 minutes. The crude reaction mixture was extracted with ether, the ether extract filtered, and the filtrate concentrated to an oil. The oil was triturated with and recrystallized from ethanol, to yield a colorless solid, m.p. 73—75° C.

B: 6-Methyl-2-(2-methyl-3-chloroanilino)-nicotinic acid

15 A solution of 9 g. of the ester of step A of this Example was refluxed with 200 ml. of methanol containing 3.3 g. of potassium hydroxide for 16 hours. The solvent was removed *in vacuo*, the residue dissolved in water and the solution neutralized with dilute hydrochloric acid, cooled and filtered. After recrystallization from benzene the product melted at 196—197° C.

25 C: Cyanomethyl 6-methyl-2-(2-methyl-3-chloroanilino)-nicotinate

The acid prepared in step B of this Example is esterified with chloroacetonitrile in the presence of trimethylamine as described in Example 2, step B.

30 D: β,γ -Isopropylidenedioxypropyl 6-methyl-2-(2-methyl-3-chloroanilino)-nicotinate

35 The cyanomethyl ester prepared in step C of this Example is transesterified with 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolan in the presence of anhydrous potassium carbonate, as described in Example 2, step C.

E: α -Glyceryl 6-methyl-2-(2-methyl-3-chloroanilino)-nicotinate

40 The β,γ -isopropylidenedioxypropyl ester prepared in step D of this Example is hydrolysed as described in Example 2, step C. β,γ -isopropylidenedioxypropyl 6-methyl-2-(2-methyl-3-nitroanilino)-nicotinate can be prepared according to Example 3, steps A—D, from ethyl 2-chloro-6-methyl-nicotinate and 2-methyl-3-nitroaniline and can be hydrolysed to α -glyceryl 6-methyl-2-(2-methyl-3-nitroanilino)-nicotinate, according to the procedure of Example 2.

EXAMPLE 4.

Glyceryl 2-(3-trifluoromethylanilino)-nicotinate

Allyl 2-(3-trifluoromethylanilino)-nicotinate is prepared by transesterification of cyanomethyl 2-(3-trifluoromethylanilino)-nicotinate according to Example 1, step B, with allyl alcohol.

A solution of 0.25 mols. of this allyl ester in 300 ml. of pyridine is cooled to 5° C and treated with a solution of 69.9 g. (0.274 mols.) of osmium tetroxide in 400 ml. of pyridine. The reaction mixture is stirred at room temperature for 24 hours, diluted with water and ether, and saturated with hydrogen sulphide. The osmium dioxide is filtered off and the desired α -glyceryl ester is isolated in the usual manner.

EXAMPLE 5.

Preparation of glyceryl 2-(3-trifluoromethylanilino)-nicotinate

A solution of 2.22 g. of 2-phenyl-1,3-dioxolan-4-yl-methyl 2-(3-trifluoromethylanilino)-nicotinate in 40 ml. of ethanol was treated with 1 g. of palladium black and hydrogen (under one and a half atmospheres pressure) at room temperature until 2 moles of hydrogen were absorbed. The catalyst was filtered off, and the filtrate was concentrated to a residue. The residue was dissolved in methanol and water was added to yield crystalline glyceryl 2-(3-trifluoromethylanilino)-nicotinate.

EXAMPLE 6.

Preparation of glyceryl 2-(3-trifluoromethylanilino)-nicotinate

Dissolve 2.22 g. of 2-phenyl-1,3-dioxolan-4-yl-methyl 2-(3-trifluoromethylanilino)-nicotinate in methylene chloride and add an excess of boron trichloride in methylene chloride at -80° C (acetone-solid carbon dioxide bath). Allow the mixture to come to room temperature, concentrate (*in vacuo*) and treat the resulting residue with methanol and then water to obtain crystalline glyceryl 2-(3-trifluoromethylanilino)-nicotinate upon filtration.

2-Phenyl-1,3-dioxolan-4-yl-methyl 2-(3-trifluoromethylanilino)-nicotinate, the starting material for Examples 5 and 6, can be prepared by transesterification of cyanomethyl 2-(3-trifluoromethylanilino)-nicotinate with 2-phenyl-1,3-dioxolan-4-yl-methanol.

According to the procedure of Example 6, 2-phenyl-1,3-dioxolan-4-yl-methyl N-(2-nitro-3,6-dichlorophenyl)-anthranilate can be converted into α -glyceryl N-(2-nitro-3,6-dichlorophenyl)-anthranilate.

The active compounds according to the invention can be administered in the form of pharmaceutical compositions comprising at least one of the said active compounds in association with a pharmaceutical carrier or excipient. Such compositions can be in a form suitable for administration by any normal route, including the oral, rectal, enteral, topical and transcutaneous routes.

Pharmaceutical compositions may for example be in solid or liquid form and are conveniently in the form of dosage units, each dosage unit providing a fixed dose of active ingredient, preferably 75 to 500 mg. Examples of dosage unit forms include tablets, dragees, capsules, lozenges and suppositories. The compositions may also be formulated as powders, granulates, suspensions, elixirs, lotions and ointments.

A total daily dosage of active ingredient within the range of 15 to 50 mg./kg. of body weight, depending upon the condition to be treated, is normally appropriate.

Compositions adapted for topical administration can be used in the treatment of local inflammation and/or irritation. Compositions adapted for internal administration can be used in the treatment of pain and inflammation, for example that associated with rheumatoid and osteoporosis joint disease, collagen disease, bursitis, gouty arthritis and spondylitis.

The following Examples A to E illustrate pharmaceutical compositions according to the invention; the compositions are prepared by standard methods. The active ingredient may be any compound according to the invention, but is preferably α -glyceryl N-(3-trifluoromethylphenyl)-anthranilate, α -glyceryl 2-(2-methyl-3-chloroanilino)-nicotinate, or α -glyceryl 2-(2-methyl-3-nitroanilino)-nicotinate.

Example A: Enteric coated tablets.

Composition of table core:	mg./core
Active ingredient, micronized	100.0
Citric acid	1.0
Lactose, USP	33.5
Dicalcium Phosphate	70.0
Pluronic F-68*	30.0
Sodium Lauryl Sulfate	15.0
Polyvinylpyrrolidone	15.0
Carbowax 1500	4.5
Carbowax 6000*	45.0
Corn Starch	30.0
Sodium Lauryl Sulfate	3.0
Magnesium Stearate	3.0

350.0

The tablets cores (prepared by standard methods) are given an enteric coating of lacquer, colored, and polished.

Pluronic F-68* is a non-ionic surface-active agent prepared by the addition of ethylene oxide to a polypropylene glycol which has a molecular weight of 1750.

Example B: Capsules.

	mg./capsule	
Active ingredient, micronized	100.00	65
Citric acid	1.00	
Pluronic F-68*	40.00	
Sodium Lauryl Sulfate	20.00	
Lactose	238.00	
Magnesium Stearate	101.00	70
	400.00	

The various ingredients are encapsulated into 2-piece gelatin capsules of suitable size.

Example C: Oral Suspension.

	mg./5ml	
Active ingredient, micronized	100.0	75
Veegum, Vanderbilt	50.0	
Standard Granulated Sugar, USP	2500.0	
Sorbitol Solution, USP	1250.0	80
Sodium Saccharin, NF	50.0	
Sodium Benzoate, USP	5.0	
Ethanol, USP	0.025 ml.	
Menthol, USP	1.000	
Flavour q.s.		85
Purified water, USP, to make	5 ml.	

Example D: Suppository

	mg./suppository	
Active ingredient, micronized	100	
Theobroma Oil, Pharm. Grade, to make	2 gms.	90

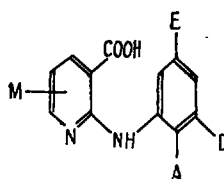
Example E: Topical Ointment

	mg./gm.	
Active ingredient, micronized	20.0	
Methylparaben, USP	0.5	95
Propylparaben, USP	0.1	
Petrolatum, USP to make	1 gm	

* "PLURONIC" and "CARBOWAX" are Registered Trade Marks.

Acids having the structure III A as defined above where A is a nitrogen atom, and derivatives thereof are the subject of claims of our British patent Nos. 1147701, 1147702 and 1147703 and our copending British patent application No. 1194246.

Thus, British patent No. 1147701 relates to 2-anilino-nicotinic acid compounds of the formula:

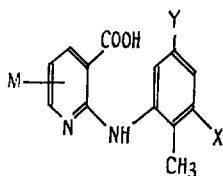


wherein M is hydrogen or lower alkyl; one of 110

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.

5 It also relates to pharmaceutically acceptable salts, esters and hydroxamic acid derivatives thereof.

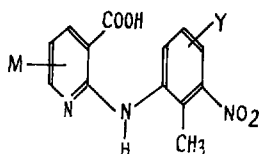
10 British Patent No. 1147702 relates to 2-anilino-nicotinic acids having the general formula



15 wherein M is a hydrogen or lower alkyl, X is chlorine or bromine, and Y is hydrogen, chloro, bromo, or lower alkyl.

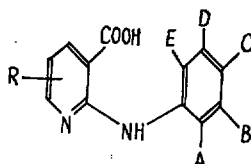
It also relates to pharmaceutically acceptable salts, esters and hydroxamic acid derivatives thereof.

20 British patent No. 1147703 relates to 2-anilino-nicotinic acids having the general formula



25 wherein M is hydrogen or lower alkyl and Y represents either a chloro, bromo, nitro, trifluoromethyl, alkyl or alkoxy substituent at the 5-position of the benzene ring or a halo, alkyl, alkoxy or trifluoromethyl substituent at the 6-position of the benzene ring, or Y represents hydrogen atoms at both the 5- and 6-positions. It also relates to pharmaceutically acceptable salts, esters, N-alkyl and N-acyl compounds and hydroxamic acid derivatives thereof.

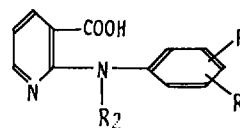
30 British Patent application No. 1194246 relates to a 2-anilino-nicotinic acid compound of the general formula



40 and its non-toxic functional derivatives, wherein R represents hydrogen, or lower alkyl, A represents hydrogen, chloro, bromo, nitro, lower alkyl or trifluoromethyl, B represents hydrogen or, in the case when at least one of A, C and E represents nitro or both A and D

represent hydrogen, then B represents hydrogen, chloro, bromo, nitro, lower alkyl or trifluoromethyl, C represents hydrogen, chloro, bromo, nitro, lower alkyl or trifluoromethyl, D represents hydrogen or, in the case when A, B, C and E represent hydrogen, then D represents nitro or, in the case when at least one of A, C, and E represents nitro, then D represents hydrogen, chloro, bromo, nitro, lower alkyl or trifluoromethyl, E represents hydrogen, chloro, bromo, nitro or trifluoromethyl; except that when either or both A and E or three of the substituents A, B, C, D and E are hydrogen, then at least one substituent in the anilino moiety must be nitro, and except that, when two only of A, B, C, D and E are hydrogen, none of the others must be alkyl. It also relates to non-toxic functional derivatives thereof including pharmaceutically acceptable acid addition salts, esters, N-alkyl, N-acyl and hydroxamic acid derivatives thereof.

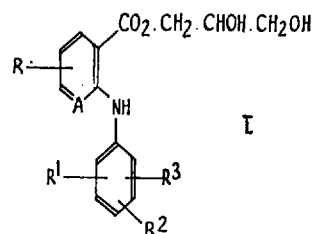
Reference is also made under Section 9 of the Patents Act to British Patent No. 1064259 which relates to a compound of the formula:



70 in which R represents a hydroxy, alkyl, haloalkyl, alkoxy, carboxy, or carboalkoxy radical, or a halogen atom, R¹ is a hydrogen atom, a hydroxy, alkyl, haloalkyl, alkoxy, carboxy, or carboalkoxy radical, or a halogen atom, and R² is a hydrogen atom or an acyl group, and the phenyl nucleus may be substituted by one or more additional alkyl radicals, and its water-soluble salts.

WHAT WE CLAIM IS:—

1. Compounds of the formula



in which

A represents a nitrogen atom or a CH group;

R represents a hydrogen atom or a methyl group;

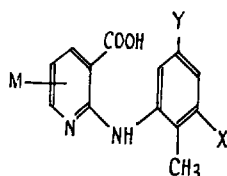
R¹ represents an alkyl, alkoxy, nitro, or trifluoromethyl group, or a halogen atom;

R² represents an alkyl, nitro, or trifluoromethyl group, or a hydrogen or halogen atom;

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

5 substituent at the 6-position of the phenyl ring. It also relates to pharmaceutically acceptable salts, esters and hydroxamic acid derivatives thereof.

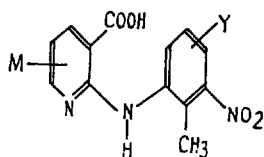
10 British Patent No. 1147702 relates to 2-anilino-nicotinic acids having the general formula



wherein M is a hydrogen or lower alkyl, X is chlorine or bromine, and Y is hydrogen, chloro, bromo, or lower alkyl.

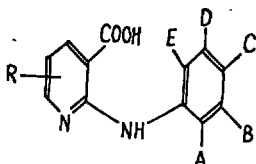
15 It also relates to pharmaceutically acceptable salts, esters and hydroxamic acid derivatives thereof.

20 British patent No. 1147703 relates to 2-anilino-nicotinic acids having the general formula



wherein M is hydrogen or lower alkyl and Y represents either a chloro, bromo, nitro, trifluoromethyl, alkyl or alkoxy substituent at the 5-position of the benzene ring or a halo, alkyl, alkoxy or trifluoromethyl substituent at the 6-position of the benzene ring, or Y represents hydrogen atoms at both the 5- and 6-positions. It also relates to pharmaceutically acceptable salts, esters, N-alkyl and N-acyl compounds and hydroxamic acid derivatives thereof.

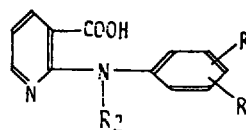
35 British Patent application No. 1194246 relates to a 2-anilino-nicotinic acid compound of the general formula



and its non-toxic functional derivatives, wherein R represents hydrogen, or lower alkyl, A represents hydrogen, chloro, bromo, nitro, lower alkyl or trifluoromethyl, B represents hydrogen or, in the case when at least one of A, C and E represents nitro or both A and D

represent hydrogen, then B represents hydrogen, chloro, bromo, nitro, lower alkyl or trifluoromethyl, C represents hydrogen, chloro, bromo, nitro, lower alkyl or trifluoromethyl, D represents hydrogen or, in the case when A, B, C and E represent hydrogen, then D represents nitro or, in the case when at least one of A, C, and E represents nitro, then D represents hydrogen, chloro, bromo, nitro, lower alkyl or trifluoromethyl, E represents hydrogen, chloro, bromo, nitro or trifluoromethyl; except that when either or both A and E or three of the substituents A, B, C, D and E are hydrogen, then at least one substituent in the anilino moiety must be nitro, and except that, when two only of A, B, C, D and E are hydrogen, none of the others must be alkyl. It also relates to non-toxic functional derivatives thereof including pharmaceutically acceptable acid addition salts, esters, N-alkyl, N-acyl and hydroxamic acid derivatives thereof.

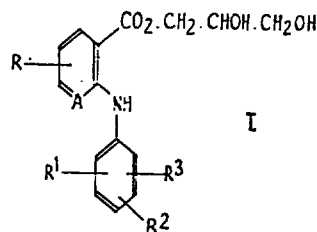
Reference is also made under Section 9 of the Patents Act to British Patent No. 1064259 which relates to a compound of the formula:



in which R represents a hydroxy, alkyl, haloalkyl, alkoxy, carboxy, or carboalkoxy radical, or a halogen atom, and R¹ is a hydrogen atom, a hydroxy, alkyl, haloalkyl, alkoxy, carboxy, or carboalkoxy radical, or a halogen atom, and R² is a hydrogen atom or an acyl group, and the phenyl nucleus may be substituted by one or more additional alkyl radicals, and its water-soluble salts.

WHAT WE CLAIM IS:—

1. Compounds of the formula



in which

A represents a nitrogen atom or a CH group;

R represents a hydrogen atom or a methyl group;

R¹ represents an alkyl, alkoxy, nitro, or trifluoromethyl group, or a halogen atom;

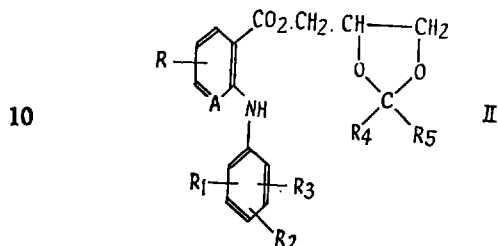
R² represents an alkyl, nitro, or trifluoromethyl group, or a hydrogen or halogen atom;



R^3 represents an alkyl, nitro, or trifluoromethyl group, or a hydrogen or halogen atom;

- 5 and the pharmaceutically acceptable cyclic acetals and ketals thereof; and the pharmaceutically acceptable salts of the compounds of the formula I and their pharmaceutically acceptable cyclic acetals and ketals.

2. Compounds of the formula

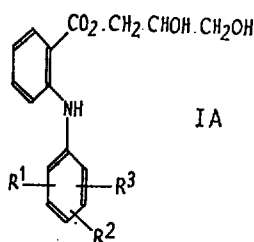


in which A, R, R^1 , R^2 , and R^3 are as hereinbefore defined, and R^4 and R^5 , which may be the same or different, represent hydrogen atoms or alkyl, aryl, or aralkyl groups, or together form a polymethylene group; and the pharmaceutically acceptable salts thereof.

- 15 3. Compounds of the formula II claimed in claim 2 in which R^4 represents a hydrogen atom or a lower alkyl group and R^5 represents a lower alkyl group; and the pharmaceutically acceptable salts thereof.

- 20 4. Salts as claimed in any of claims 1 to 3 formed with maleic, salicylic, succinic, methylsulfonic, tartaric, citric, hydrochloric, hydrobromic, sulfuric, or phosphoric acid.

5. Compounds of the formula



in which

- 30 R^1 represents a lower alkyl, lower alkoxy, nitro, or trifluoromethyl group, or a halogen atom;

R^2 represents a lower alkyl, nitro, or trifluoromethyl group, or a hydrogen or halogen atom; and

- 35 R^3 represents a lower alkyl, nitro, or trifluoromethyl group, or a hydrogen or halogen atom.

- 40 6. Compounds as claimed in claim 5 in which R^1 is lower alkyl, R^2 is hydrogen, and R^3 is halogen.

7. α -Glyceryl N-(3-trifluoromethylphenyl)-anthranilate.

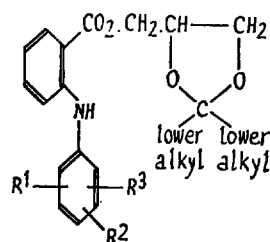
8. α -Glyceral N-(2-methyl-3-chlorophenyl)-anthranilate.

- 45 9. α -Glyceryl N-(2-methyl-3-nitrophenyl)-anthranilate.

10. α -Glyceryl N-(2-methyl-3-trifluoromethylphenyl)-anthranilate.

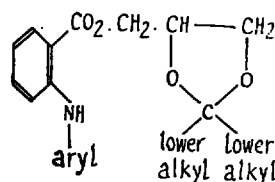
11. The pharmaceutically acceptable cyclic acetals and ketals of the compounds claimed in claim 5.

12. Compounds of the formula

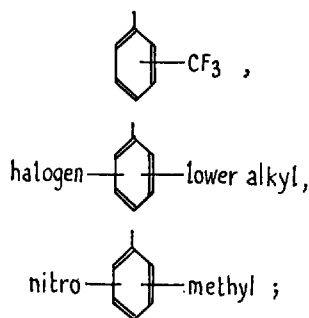


in which R^1 , R^2 and R^3 are as defined in claim 5.

13. Compounds of the formula



in which the group designated "aryl" has the formula



14. Compounds as claimed in claim 13 in which all the lower alkyl groups are methyl groups.

15. β,γ -Isopropylidenedioxypropyl N-(3-trifluoromethylphenyl)-anthranilate.

16. β,γ -Isopropylidenedioxypropyl N-(2-methyl-3-chlorophenyl)-anthranilate.

17. β,γ -Isopropylidenedioxypropyl N-(2-methyl-3-nitrophenyl)-anthranilate.

18. β,γ -Isopropylidenedioxypropyl N-(2-methyl-3-trifluoromethylphenyl)-anthranilate.

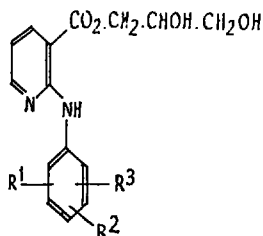
19. Pharmaceutically acceptable acid-addition salts of the compounds claimed in any of claims 5 to 18.

20. Salts as claimed in claim 19 formed with maleic, salicylic, succinic, methylsulfonic, tartaric, citric, hydrochloric, hydrobromic, sulfuric or phosphoric acid.





21. Compounds of the formula



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in which

5 R^1 represents a lower alkyl, lower alkoxy, nitro or trifluoromethyl group, or a halogen atom;

R^2 represents a lower alkyl or trifluoromethyl group, or a hydrogen or halogen atom; and

10 R^3 represents a lower alkyl or trifluoromethyl group, or a hydrogen or halogen atom.

22. Compounds as claimed in claim 21 in which R^1 is nitro or halogen, R^2 is lower alkyl, and R^3 is hydrogen.

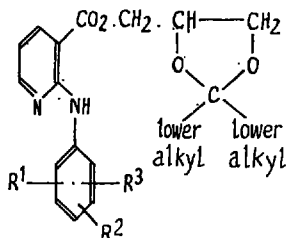
23. α -Glyceryl 2-(2-methyl-3-chloroanilino)-nicotinate.

24. α -Glyceryl 2-(2-methyl-3-nitroanilino)-nicotinate.

20 25. α -Glyceryl 2-(2-methyl-3-trifluoromethylanilino)-nicotinate.

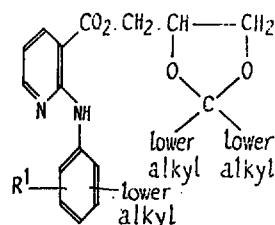
26. The pharmaceutically acceptable cyclic acetals and ketals of the compounds claimed in claim 21.

25 27. Compounds of the formula



in which R^1 , R^2 and R^3 are as defined in claim 21.

28. Compounds of the formula



in which R^1 is nitro or halogen.

29. Compounds as claimed in claim 28 in which all the lower alkyl groups are methyl groups.

30 30. β,γ -Isopropylidenedioxypropyl 2-(2-methyl-3-chloroanilino)-nicotinate.

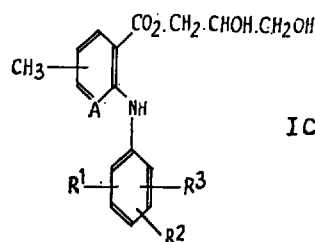
31. β,γ -Isopropylidenedioxypropyl 2-(2-methyl-3-nitroanilino)-nicotinate.

32. β,γ -Isopropylidenedioxypropyl 2-(2-methyl-3-trifluoromethylanilino)-nicotinate.

33. Pharmaceutically acceptable acid addition salts of the compounds claimed in any of claims 21 to 32.

34. Salts as claimed in claim 33 formed with maleic, salicylic, succinic, methylsulfonic, tartaric, citric, hydrochloric, hydrobromic, sulfuric or phosphoric acid.

35. Compounds of the formula



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in which R^1 , R^2 and R^3 are as defined in claim 21, and A represents a nitrogen atom or the group CH.

36 Compounds as claimed in claim 35 in which R^1 , R^2 and R^3 are as defined in claim 22.

37 α -Glyceryl 6-methyl-2-(2-methyl-3-chloroanilino)-nicotinate.

38. α -Glyceryl 6-methyl-2-(2-methyl-3-nitroanilino)-nicotinate.

39. The pharmaceutically acceptable cyclic acetals and ketals of the compounds claimed in claim 35.

40. β,γ -Isopropylidenedioxypropyl 6-methyl-2-(2-methyl-3-chloroanilino)-nicotinate.

41. β,γ -Isopropylidenedioxypropyl 6-methyl-2-(2-methyl-3-nitroanilino)-nicotinate.

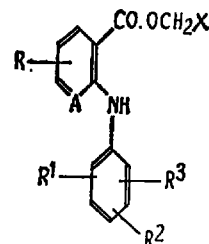
42. Pharmaceutically acceptable acid addition salts of the compounds of claims 35 to 41.

43. Salts as claimed in claim 42 formed with maleic, salicylic, succinic, methylsulfonic, tartaric, citric, hydrochloric, hydrobromic, sulfuric or phosphoric acid.

44. The compounds listed in Table I herein.

45. The compounds listed in Table II herein.

46. Process for the preparation of a compound of the formula



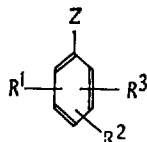
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in which X represents an α,β -dihydroxy-ethyl group or a cyclic acetal or ketal thereof, and A, R, R^1 , R^2 and R^3 are as defined in claim

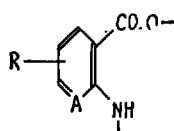
1, which comprises condensing a compound of the formula



5 by known methods with a compound of the formula



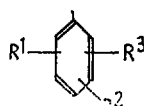
10 in which R¹, R² and R³ are as defined in claim 1, X¹ represents the group X hereinbefore defined or a vinyl or epoxyethyl group, Y and Z represent reactive groups capable of condensing during the reaction to leave the bridge



15 (in which R and A are as defined in claim 1) between the the groups



(in which X¹ is as hereinbefore defined) and



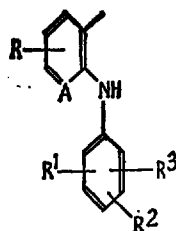
20 (in which R¹, R² and R³ are as defined in claim 1; and, where X¹ represents a vinyl or epoxyethyl group, converting the product by known methods of oxidation and/or hydrolysis into a β,γ-dihydroxypropyl ester.

25 47. Process for the preparation of a compound claimed in claim 1 which comprises reacting a compound of the formula



or an ester-forming derivative thereof.

wherein P represents the grouping



30

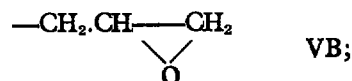
in which A, R, R¹, R² and R³ are as defined in claim 1, with a compound of the formula HO.Q, or an ester-forming derivative thereof;

wherein Q represents one of the following groups:

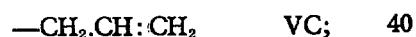
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or a cyclic ketal or acetal thereof:



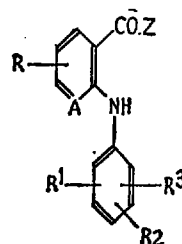
and



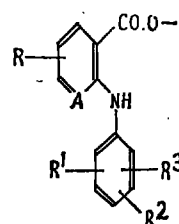
and thereafter, where Q represents formula VB or VC, oxidising and/or hydrolysing the product as necessary to a β,γ-dihydroxypropyl ester.

48. A process as claimed in claim 47 in which an acid halide of a compound of the formula III A is reacted with a compound of the formula HO.Q. 45

49. A process as claimed in claim 47 in which a compound of the formula HO.Q is reacted with a compound of the formula 50



in which A, R, R¹, R² and R³ are as defined in claim 1 and Z is a chlorine atom or one of the groups: 55



(in which A, R, R¹, R² and R³ are as defined in Claim 1), and



50. A process as claimed in claim 47 in which a compound of the formula III A is condensed with glycerol or a cyclic ketal or acetal thereof, allyl alcohol, or epoxypropyl alcohol, in the presence of a dehydrating agent. 60

51. A process as claimed in claim 50 in which the dehydrating agent is a carbodi-imide or an α-alkynylamine. 65

52. A process as claimed in claim 51 in which the carbodi-imide is dicyclohexylcarbodi-imide. 70

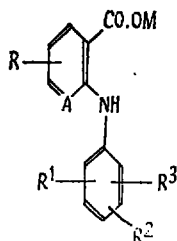


67. A process as claimed in claim 47 in which a compound of the formula IIIA is condensed with a compound of the formula

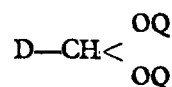
57. A process as claimed in claim 56 in
20 which the reactive ester has the formula



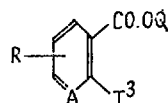
63. A process as claimed in claim 47 in
40 which a compound of the formula



W.Q



69. A process for the preparation of a 65
compound as claimed in claim 1 which comprises reacting a compound of the formula

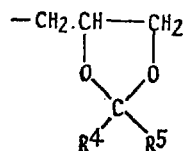


A benzene ring with four substituents: R^1 at the 1-position, R^2 at the 3-position, R^3 at the 4-position, and T^4 at the 6-position.

74. A process as claimed in any of claims 47 to 73 in which Q represents a cyclic ketal or acetal of a group of the formula VA in claim 47.



75. A process as claimed in claim 74 in which Q has the formula



5 in which R⁴ and R⁵, which may be the same or different, represent hydrogen atoms or alkyl, aryl, or aralkyl groups, or together form a polymethylene group.

76. A process as claimed in claim 75 in which Q is a β,γ -isopropylidenedioxypopyl group.

77. A process as claimed in any of claims 47 to 76 in which, where Q represents formula VB in claim 47, the hydrolysis of the epoxide ring is effected by means of ring-opening with *p*-nitrobenzoic acid and hydrolysis of the resulting *p*-nitrobenzoate ester.

78. A process as claimed in any of claims 47 to 76 in which, where Q represents formula VC in claim 47, the oxidation is effected by means of osmium tetroxide substantially in the absence of other oxidising agents.

79. A process as claimed in any of claims 47 to 76 in which, where Q represents formula VC in claim 47, the oxidation is effected by means of potassium permanganate, or silver chlorate and osmium tetroxide, or hydrogen peroxide and osmium tetroxide, or hydrogen peroxide and selenium dioxide, or silver iododibenzoate and hydrolysis, or an organic peroxy acid followed by transformation of the resulting epoxide into the dihydroxypropyl ester.

80. A process as claimed in claim 79 in which said transformation is effected by means of reaction of the epoxide with *p*-nitrobenzoic acid, followed by hydrolysis.

81. A process as claimed in any of claims 47 to 80 in which, where a cyclic ketal or acetal of a glyceryl ester of the formula I defined in claim 1 is required and the product is the α -glyceryl ester itself, this product is reacted with the appropriate aldehyde or ketone in the presence of a condensing agent.

82. A process as claimed in any of claims 47 to 76 in which, where the α -glyceryl ester of the formula I as defined in claim 1 is required and the product is a cyclic ketal or acetal thereof, the acetal or ketal is converted by known methods into the α -glyceryl ester.

83. A process as claimed in any of claims 47 to 76 in which, where the α -glyceryl ester of the formula I defined in claim 1 is required and the product is a cyclic ketal or acetal thereof, the ketal or acetal is selectively hydrolysed to the α -glyceryl ester.

84. A process as claimed in claim 83 in which the hydrolysis is effected under mildly acidic conditions.

85. A process as claimed in any of claims 47 to 76 in which, where the α -glyceryl ester of the formula I defined in claim 1 is required and the product is a cyclic ketal or acetal thereof, the ketal or acetal is cleaved to the α -glyceryl ester by reaction with boron trichloride at reduced temperature, followed by hydrolysis of the resulting borate complex.

86. A process as claimed in any of claims 47 to 76 in which, where the α -glyceryl ester of the formula I defined in claim 1 is required and the product is a cyclic acetal or ketal (dioxolan) thereof, the dioxolan ring being cleavable by hydrogenation, the dioxolan is cleaved to the required α -glyceryl ester by hydrogenation.

87. A process as claimed in claim 86 in which the dioxolan is formed with an aldehyde of the formula



in which R⁵ represents an aromatic group.

88. A process as claimed in claim 87 in which R⁵ represents a phenyl group.

89. A process as claimed in any of claims 47 to 88 in which, where a compound of the formula I defined in claim 1 or cyclic ketal or acetal thereof is required and the product is an acid addition salt thereof, the salt is converted into the compound of formula I or ketal or acetal thereof by reaction with a base.

90. A process as claimed in any of claims 47 to 88 in which, where the product is a compound of the formula I defined in claim 1 or cyclic acetal or ketal thereof, and a pharmaceutically acceptable acid addition salt thereof is required, the compound of the formula I or acetal or ketal thereof is converted into a pharmaceutically acceptable acid addition salt.

91. A process as claimed in claim 90 in which the acid is maleic, salicylic, succinic, methylsulfonic, tartaric, citric, hydrochloric, hydrobromic, sulfuric, or phosphoric acid.

92. A process for the preparation of α -glyceryl esters of the formula I defined in claim 1 and cyclic acetals and ketals thereof and salts thereof substantially as herein described.

93. α -Glyceryl esters of the formula I defined in claim 1 and cyclic acetals and ketals thereof and salts thereof whenever produced by a process as claimed in any of claims 47 to 92.

94. Pharmaceutical compositions comprising an active ingredient at least one compound selected from α -glyceryl esters of the formula I defined in claim 1, and the pharmaceutically acceptable cyclic acetals and ketals thereof, and the pharmaceutically acceptable salts of said compounds of the formula I and cyclic acetals and ketals thereof, together with a pharmaceutical carrier or excipient.



95. Compositions as claimed in claim 94 in the form of dosage units.
96. Compositions as claimed in claim 95 in the form of tablets, capsules, dragees, suppositories or lozenges.
97. Compositions as claimed in claim 95 or claim 96 containing from 75 to 500 mg. of active ingredient.
98. Compositions as claimed in claim 94 in the form of ointments, suspensions or elixirs.
99. Compositions as claimed in any of claims 94 to 98 in which the active ingredient is α -glyceryl 2-(2-methyl-3-chloroanilino)-nicotinate.
100. Compositions as claimed in any of claims 94 to 98 in which the active ingredient is α -glyceryl 2-(2-methyl-3-nitroanilino)-nicotinate.
101. Compositions as claimed in any of claims 94 to 98 in which the active ingredient is α -glyceryl 6-methyl-2-(2-methyl-3-chloroanilino)-nicotinate.
102. Compositions as claimed in any of claims 94 to 98 in which the active ingredient is α -glyceryl 6-methyl-2-(2-methyl-3-nitroanilino)-nicotinate.
103. Compositions as claimed in any of claims 94 to 98 in which the active ingredient is α -glyceryl N-(2-methyl-3-chlorophenyl)-anthranilate.
- 104 Compositions as claimed in any of claims 94 to 98 in which the active ingredient is α -glyceryl N-(3-trifluoromethylphenyl)-anthranilate.
105. Compositions as claimed in any of claims 94 to 98 in which the active ingredient is α -glyceryl N-(2-methyl-3-nitrophenyl)-anthranilate.
106. Compositions as claimed in any of claims 94 to 98 in which the active ingredient is α -glyceryl N-(2-methyl-3-trifluoromethylphenyl)-anthranilate.
- 107 Compositions as claimed in any of claims 92 to 94 in which the active ingredient is α -glyceryl 2-(2-methyl-3-trifluoromethyl-anilino)-nicotinate.
108. Compositions as claimed in any of claims 94 to 98 in which the active ingredient is a pharmaceutically acceptable acid addition salt of a compound claimed in any of claims 7 to 10, 23, 24, 25, 37 and 38.
109. A pharmaceutical composition according to claim 94 and substantially as hereinbefore described and exemplified.
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