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3,475,427

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3,475,427

PHENOXAZINES

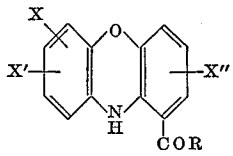
Benjamin Blank, Trevose, and Blaine M. Sutton, Philadelphia, Pa., assignors to Smith Kline & French Laboratories, Philadelphia, Pa., a corporation of Pennsylvania

No Drawing. Filed Feb. 3, 1966, Ser. No. 524,828
Int. Cl. C07d 87/50
U.S. Cl. 260—244 9 Claims

ABSTRACT OF THE DISCLOSURE

This invention comprises novel substituted phenoxazinyl-1-carboxylic acid derivatives together with methods and intermediates for making said derivatives. The new compounds of this invention have novel biological activity, such as anti-inflammatory, antipyretic, antiviral and analgetic activities as well as utility as intermediates for preparing other biologically active phenoxazine compounds for example phenoxazines having antihistamine or tranquilizing activity.

The compounds having the following structural formula are illustrative of the novel phenoxazinyl-1-carboxylic acids of this invention:



Formula I

in which:

R represents alkoxy of 1 to 18 carbon atoms, dialkylaminoalkoxy said alkyl being of 1 to 3 carbon atoms and said alkoxy being of 2 to 4 carbon atoms, NR_1R_2 or, most advantageously, hydroxy.

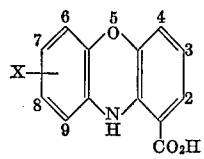
R_1 and R_2 represent hydrogen, lower alkyl of 1 to 6 carbon atoms, phenyl or dialkylaminoalkylene said alkyl being of 1 to 3 carbon atoms and said alkylene being of 2 to 4 carbon atoms.

X and X′ represent trifluoromethyl, halo such as chloro, bromo or fluoro, trifluoromethoxy, methoxy, ethoxy, nitro, trifluoromethylthio, sulfamyl, N-methylsulfamyl, N,N-dimethylsulfamyl, methylthio, methylsulfoxy, trifluoromethylsulfoxy, methyl, ethyl, carbamyl, N-methylcarbamyl, N,N-dimethylcarbamyl, methylsulfonyl, trifluoromethylsulfonyl or hydrogen at least one of X and X′ being a substituent other than hydrogen; and

X″ represents hydrogen or when X and X′ are hydrogen trifluoromethyl or halo such as chloro, bromo or fluoro.

Compounds containing a single strongly electronegative substituent on the phenoxazine ring in addition to the essential 1′-carboxy function are preferred. Exemplary of such substituents are trifluoromethyl, bromo, fluoro, chloro or trifluoromethylsulfonyl.

Most advantageous are compounds of the structural formula:



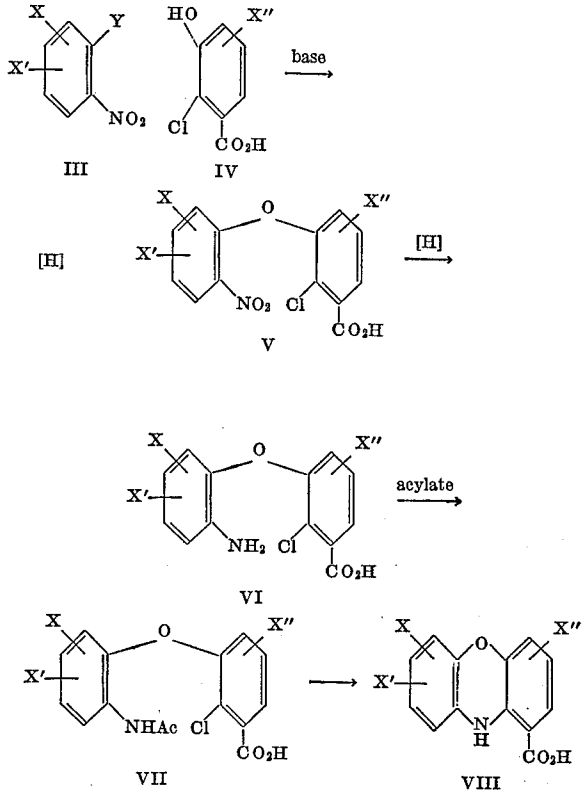
Formula II

in which X is a strongly electronegative substituent, preferably in the 7, 8 or 9-position, such as chloro, bromo, fluoro, trifluoromethylsulfoxy or preferably trifluoromethyl.

It has been found for example that the most active new compound of this new series with respect to anti-inflammatory activity is 8-trifluoromethylphenoxazine-1-carboxylic acid. We have unexpectedly discovered that it is necessary for anti-inflammatory activity to have the carboxy function at the 1-position of these phenoxazine compounds and to have at least one ring substitutent especially an electronegative one. N-substitution of the phenoxazinyl ring often decreases the activity somewhat.

Also included in this invention are the salt derivatives of the compounds represented above, for example in the carboxylic acid series itself the salts with pharmaceutically acceptable organic or inorganic bases such as the ammonium or alkali metal salts including the potassium, sodium or calcium salts. When the claimed compound has a basic center, nontoxic acid addition or quaternary ammonium salts with pharmaceutically acceptable acids or quaternizing agents are included such as those acid addition salts formed with hydrochloric, sulfuric, sulfamic, ethandisulfonic, maleic, hydrobromic or phosphoric acids as well as quaternary salts formed by lower alkyl chloride, bromide or iodides, benzylchloride, ethyl tosylate, methyl sulfate, etc. Such salt derivatives are prepared by standard reactions well-known to the skilled chemist, such as reacting the acid compound with a standard alkali or amine base in neutral solution or with an active alkali metal; reacting the basic compound with an excess of the desired acid or quaternizing compound in suitable solvent. Also included in this invention are the N-acyl derivatives such as the N-lower alkanoyl derivatives which may be isolated as intermediates in the cyclization reaction.

The compounds of this invention are prepared by the following method:



III IV V VI VII VIII

in which Ac represents a convenient low molecular weight acyl group, such as propionyl, acetyl or preferably the easily removed formyl; Y represents a reactive halo atom such as fluoro, bromo, chloro or iodo; and the other symbols are as described. The chloro intermediates (III, Y=Cl) are particularly useful but can also be fluoro,

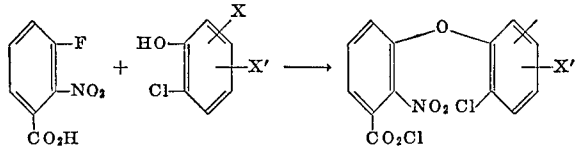
bromo or iodo. The other symbols are as previously defined.

The chemical reaction described above (III→VIII) is similar to that disclosed in U.S. Patent No. 2,947,746 but is characterized by the presence of the 1-carboxy function in the end product. The starting materials for this process are novel optionally substituted 2-halo-3-(2'-amino, acetamido or formamidophenoxy)benzoic acids (VII) which are reacted at elevated temperatures in the presence of a base such as an alkali metal carbonate and a copper catalyst such as cuprous carbonate, copper, bronze or copper powder in a suitable solvent preferably dimethylformamide or dimethylacetamide. The reaction is usually run at reflux temperature. The 2'-formamidophenoxy benzoic acids are preferably used because the N-formyl group is easily removed during the reaction but the higher acylamido groups are more stable thereby necessitating stronger hydrolysis conditions to remove the N-acyl group from the N-acylated phenoxazinyl-1-carboxylic acid intermediates to obtain the desired substituted phenoxazinyl-1-carboxylic acid of Formula I.

The phenoxybenzoic acid intermediates of Formulae V, VI and VII are new compounds and are a part of this invention.

The 2-halo-3-(2'-nitrophenoxy) benzoic acids are prepared from known or easily prepared starting materials by condensing an optionally substituted 2-halonitrobenzene with a 2-halo-3-hydroxybenzoic acid in the presence of base in suitable inert solvent, such as a lower alcohol, dimethylfomamide, dimethylacetamide, or diglyme (bis (2-methoxyethyl) ether) to give the desired 2'-nitrophenoxybenzoic acids (V). These compounds are then reduced by chemical reduction usually using iron-acetic acid to give the 2'-amines (VI) which are in turn N-acylated by standard reactions such as heating in commercial formic acid, methyl formate or using the more common acyl halide or anhydride reactions to give the N-acyl starting materials (VII).

Alternatively the substituents in the phenoxazinyl ring not containing the 1-carboxy group may be present in the phenolic starting material such as in the following reactions:



IX X XI

as described for Formulae V to VIII. The phenoxybenzoic acid intermediates (XI→XIII) are a part of this invention.

In this sequence of reactions the key intermediate is 3-fluoro-2-nitrobenzoic acid (IX), a new compound which has been found to possess a reactive fluoro atom which unexpectedly enters into the condensation reaction readily to give the 3-(2'-halophenoxy)-2-nitrobenzoic acids (XI) which are reduced, N-acylated and cyclized as described previously. This reaction sequence is of considerable interest because of the easy accessibility of substituted 2-halophenols (X). It should be noted that the 3-bromo or 3-chloro-2-nitrobenzoic acids do not react appreciably in the condensation reaction.

While the reactions above are demonstrated with the 1-carboxyphenoxazine, the various desired ester derivatives of the 1-carboxy function can be similarly prepared.

Alternatively the carboxylic ester derivatives may be prepared by direct esterification of the phenoxazinyl-1-carboxylic acid by standard methods, most conveniently by using the phenoxazinyl-1-carbonyl chloride.

Finally, certain of these novel compounds are conveniently prepared by direct metallation and carbonation of the substituted phenoxazine, such as using an alkyl or aryl lithium compound for example n-butyl lithium to give the organometallic compound, followed by carbonation to give the desired substituted phenoxazinyl-1-carboxylic acid.

The compounds of this invention are of particular utility for their biological activity, for example, for various anti-inflammatory, antipyretic, antiviral and analgetic (in pressure based tests) activities. Certain of these compounds also have anthelmintic, antitubercular and antifungal activity as do the phenoxazines disclosed by French Patent No. 1,336,070.

The anti-inflammatory activity of these compounds is particularly unexpected. The compounds are administered internally either subcutaneously or preferably orally in an amount to induce the desired biological activity. Often the compound is administered in unit doses such as from about 5 mg. to 250 mg. from one to five times daily. Most conveniently, the compound is combined with a standard pharmaceutical filler and administered orally as a capsule, tablet, troche, liquid or suspension or parenterally as a sterile suspension.

One of the unexpected aspects of this discovery is the low incidence of side effects especially in the ulcerogenic area common with the few non-steroidal anti-inflammatory agents known in the prior art. The claimed compounds also have little central nervous system activity at effective anti-inflammatory doses.

As examples of the anti-inflammatory activity of these compounds the following test results were obtained:

8-TRIFLUOROMETHYLPHENOXAZINYL-1-CARBOXYLIC ACID

Filter paper granuloma, active at 10 mg./kg. subcutaneously in rats.

Ultraviolet-induced erythema, active at 40.0 mg./kg. orally in guinea pigs.

8-CHLOROPHENOXAZINYL-1-CARBOXYLIC ACID

Filter paper granuloma, active at 20 mg./kg. subcutaneously in rats.

Ultraviolet-induced erythema, active at 40 mg./kg. orally in guinea pigs.

7-TRIFLUOROMETHYLPHENOXAZINYL-1-CARBOXYLIC ACID

Filter paper granuloma, active 80 mg./kg. subcutaneously in rats.

The following examples are designed to illustrate the preparation of the compounds of this invention but not to limit the scope of the invention.

Example 1

A mixture of 71.6 g. (0.32 mole) of 2-chloro-5-trifluoromethyl-nitrobenzene, 54.6 g. (0.32 mole) of 2-chloro-3-hydroxybenzoic acid, 41.4 g. (0.64 mole) of potassium hydroxide and 1.2 l. of ethanol is stirred under reflux for 24 hours. The cooled reaction mixture is poured into 5 l. of an ice-water slurry, stirred, cooled and filtered to give 2 - chloro-3-(2'-nitro-4'-trifluoromethylphenoxy) benzoic acid, M.P. 209–210° C.

This compound (55.0 g., 0.152 mole) together with 42.6 g. (0.76 atom) of iron, 900 ml. of 3:1 ethanol-water and 91.4 g. (87 ml., 1.52 moles) of glacial acetic acid is reacted then stirred at reflux for two hours. The cooled reaction mixture is made basic with ammonium hydroxide then swept with air bubbles for 8 hours. The filtered mixture is evaporated as reduced pressure, diluted with water and neutralized with dilute hydrochloric acid to give 2-chloro-3-(2'-amino-4'-trifluoromethyl phenoxy) benzoic acid, M.P. 138–139° C.

A mixture of 34.0 g. (0.103 mole) of the amino compound and 350 ml. of 97–100% formic acid is heated at reflux for 3 hours then poured into 5 l. of ice-water slurry to give after purification 2-chloro-3-(2'-formamido-4'-trifluoromethylphenoxy) benzoic acid, M.P. 200–201° C.

A mixture of 31.6 g. (0.88 mole) of the formamido compound, 14.75 g. of potassium carbonate, 1.8 g. of copper powder and 450 ml. of dry dimethylformamide is stirred under reflux for two hours under nitrogen. The hot mixture is filtered into several volumes of hot water and acidified. The crude 8-trifluoromethylphenoxazinyl-1-carboxylic acid is cooled, separated, and recrystallized from acetonitrile, M.P. 263–265° C.

An aliquot of 8-trifluoromethylphenoxazinyl-1-carboxylic acid in acetonitrile-ether is shaken with a few drops of sodium methoxide solution to give the sodium salt, with ammonia or ethylamine to give the ammonium or ethylamine salts.

Example 2

A mixture of 17.25 g. of 2-chloro-3-hydroxybenzoic acid (M.P. 244–245° C.), the amino compound (M.P. g. of sodium hydroxide, 25 ml. of water, and 200 ml. of diglyme is reacted for 65 hours and worked up as described above to give 2-chloro-3-(2′-nitro-4′-sulfamylphenoxy) benzoic acid, M.P. 228–229° C. This compound (23.75 g.) is reduced with iron-acetic acid-aqueous alcohol as described to give 3-(2′-amino-4′-sulfamylphenoxy)-2-chlorobenzoic acid, M.P. 208–210° C., of which 12.0 g. is N-formylated to give 2-chloro-3-(2′-formamido-4′-sulfamylphenoxy) benzoic acid, M.P. 149–151° C.

The formamido compound (10.5 g.) is heated under reflux for 1½ hours with 5.5 g. of potassium carbonate, 0.59 g. of copper and 175 ml. of dimethylformamide to give 8-sulfamylphenoxazinyl-1-carboxylic acid, M.P. 263–265° C.

Example 3

Substituting 18.2 g. (0.077 mole) of 2-chloro-5-methylsulfonylnitrobenzene in Example 1 gives in succession 2-chloro-3-(4′-methylsulfonyl - 2′ - nitrophenoxy) benzoic acid (M.P. 244–245° C.), the amino compound, (M.P. 141–143° C.), the formamide (M.P. 216–218° C.) and 8-methylsulfonylphenoxazinyl - 1 - carboxylic acid (M.P. 273–274° C.).

Example 4

Substituting 5.15 g. (0.03 mole) of 2-chloro-5-methylnitrobenzene using sodium hydroxide and refluxing for 90 hours gives 2-chloro-3-(2′-nitro-4′-tolyloxy) benzoic acid (M.P. 173–175° C.), 3-(2′-amino-4′-tolyloxy)-2-chlorobenzoic acid (M.P. 135–136° C.), the formamide (M.P. 198–199° C.) and finally 8-methylphenoxazinyl-1-carboxylic acid (M.P. 264–266° C.).

Example 5

Substituting 6.1 g. (0.03 mole) of 2-chloro-5-methylthionitrobenzene gives 2-chloro-3-(4′-methylthio-2′-nitrophenoxy)-benzoic acid (M.P. 180–182° C.), the amine (M.P. 120–122° C.), the formamide (M.P. 184–186° C.), and finally 8-methylthiophenoxazinyl-1-carboxylic acid (M.P. 253–254° C.).

Example 6

Substituting 26.0 g. (0.15 mole) of 4-chloro-N,N-dimethyl-3-nitrobenzenesulfonamide gives the nitro compound (M.P. 180–181° C.), the amine (M.P. 202–204° C.), the formamide (M.P. 141–143° C.), and finally 8-dimethylsulfamylphenoxazinyl-1-carboxylic acid (M.P. 281–283° C.).

Example 7

Substituting 31 g. (0.2 mole) of 4-chloro-N-methyl-3-nitrobenzenesulfonamide gives the benzoic acid (M.P. 197–199° C.), the amine, the formamido (M.P. 188–190° C.) and finally 8-methylsulfamylphenoxazinyl-1-carboxylic acid.

Example 8

A mixture of 3.6 g. (0.01 mole) of 2-bromo-3-(2′-formamido-4′-trifluoromethylphenoxy) benzoic acid, 1.9 g. of potassium carbonate, 0.12 g. of cuprous carbonate and 50 ml. of xylene is heated at reflux over a water separator for 21 hours. The reaction is worked up by the standard methods to give 8-trifluoromethylphenoxazinyl-1-carboxylic acid (34%).

Example 9

A mixture of 14.8 g. (0.086 mole) of 2-chloro-3-hydroxybenzoic acid, 23.3 g. (0.86 mole, B.P. 67–72° C. at 6.6 mm. from diazotization of 2-nitro-5-trifluoromethylaniline) of 3-bromo-4-nitrobenzotrifluoride, 9.70 g. (0.172 mole) of potassium hydroxide and 400 ml. of dry ethanol is heated at reflux for two days then worked up as described to give 2-chloro-3-(2′-nitro-5′-trifluoromethylphenoxy)-benzoic acid, M.P. 176–177° C. In succession, the amine (M.P. 147–148° C.), the formamide (M.P. 178–179° C.) and finally 7-trifluoromethylphenoxazinyl-1-carboxylic acid, M.P. 238–239° C., are obtained.

Example 10

Using 25 g. of 2,3-dichloronitrobenzene, 22.5 g. of 2-chloro-3-hydroxybenzoic acid, 16.9 g. of potassium hydroxide in 300 ml. of ethanol gives 2-chloro-3-(2′-chloro-5′-nitrophenoxy) benzoic acid (M.P. 201–202° C.), the amine (M.P. 158–159° C.), the formamide, and finally 6-chlorophenoxazinyl - 1 - carboxylic acid (M.P. 283–285° C.).

Example 11

Using 42.0 g. of 2,4-dichloronitrobenzene and 31 g. of 2-chloro-3-hydroxybenzoic acid gives the phenoxybenzoic acid (M.P. 213–214° C.), the amine (M.P. 214–217° C.), the formamide (M.P. 198–200° C.), and, using copper-bronze catalyst, 7 - chlorophenoxazinyl-1-carboxylic acid (M.P. 290–291° C.).

Example 12

Using 25 g. of 2,5-dichloronitrobenzene and 22.5 g. of 2-chloro-3-hydroxybenzoic acid gives the phenoxybenzoic acid (M.P. 204–205° C.), the amine (M.P. 182–183° C.), the formamide (M.P. 229–230° C.), and 8-chlorophenoxazinyl-1-carboxylic acid (M.P. 276–277° C.).

Example 13

Using 29.4 g. of 2,4,5-trichloronitrobenzene gives the phenoxybenzoic acid (M.P. 179–180° C.), the amine (M.P. 205–206° C.), the formamide (M.P. 228–230° C.) and 7,8 - dichlorophenoxazinyl-1-carboxylic acid (M.P. 331–333° C.).

Example 14

Using 25 g. of 2 - bromo-5-trifluoromethylsulfonylnitrobenzene and 12.9 g. of 2-chloro-3-hydroxybenzoic acid in alkaline ethanol and benzene gives the phenoxybenzoic acid (M.P. 162–164° C.), the amine (M.P. 173–174° C.), the formamide (M.P. 170–171° C.), and 8-trifluoromethylsulfonylphenoxazinyl-1-carboxylic acid, M.P. 272–273° C.

Example 15

A stirred solution of 5.6 g. of 2 - trifluoromethylphenoxazine in 500 ml. of ether is added to a solution of 3 molar equivalents of n-butyl lithium. The mixture is allowed to stand overnight then poured onto an ether-Dry Ice slurry. After standing for one hour water is added. The acidified mixture is then separated. The ether phases are combined and extracted with dilute base. The basic extracts are acidified to give 2-trifluoromethylphenoxazinyl-1-carboxylic acid.

Substituting 2-fluorophenoxazine, 2-bromophenoxazine or 2-chlorophenoxazine gives the corresponding 1-carboxy derivatives in low yield.

Example 16

2-nitro-3-trifluoromethylaniline (70 g., 0.33 mole) is added to 300 ml. of cooled concentrated hydrochloric with stirring. A solution of 26 g. of sodium nitrite in 60 ml. of water is added keeping the temperature below 10° C.

The cooled solution is filtered. The filtrate is diluted with 250 ml. of 48% fluoboric acid and cooled.

The salt which separates is dried and added in small portions to stirred mineral oil at 125–130° C. After complete reaction, the temperature is raised to 150° C. and the nitrofluorobenzotrifluoride is distilled away from the oil. A mixture of 3-fluoro-2-nitrobenzotrifluoride and 80% sulfuric acid is stirred and heated at 125° C. for 2 hours. The mixture is cooled, poured into ice-water then cooled to give the desired 3-fluoro-2-nitrobenzoic acid, a novel and important intermediate.

A mixture of 18.5 g. of the benzoic acid, 19.6 g. of 2-chloro-5-trifluoromethylphenol [Mooradian, J. Am. Chem. Soc. 73, 3470 (1951)] and 8 g. of sodium hydroxide in 750 ml. of dimethylformamide is stirred under reflux for 6 hours. The mixture is cooled and quenched to give 2-nitro - 3 - (2' - chloro - 5' - trifluoromethylphenoxy) benzoic acid. This compound (19 g.) is reduced with iron-acetic acid as in Example 1 to give 2-amino-3-(2'-chloro-5'-trifluoromethylphenoxy) benzoic acid.

The amino compound (12 g.) is heated at reflux in 150 ml. of formic acid solution for 4 hours. Quenching gives the N-formyl derivative. This compound (9.5 g.) is stirred with 4 g. of potassium carbonate and 0.5 g. of bronze powder in dimethylacetamide at reflux for 4 hours. Quenching and acidification gives 7-trifluoromethylphenoxazinyl-1-carboxylic acid.

Example 17

Using the reaction conditions and reactions of Example 16, the following phenolic compounds are condensed with 3-fluoro-2-nitrobenzoic acid:

2,4-dichloro-3-trifluoromethylphenol to give 2-nitro-3-(2',4' - dichloro-3'-trifluoromethylphenoxy) benzoic acid, the 2-amino, the 2-formamido and finally 8-chloro-9-trifluoromethylphenoxazinyl-1-carboxylic acid.

2,5-dichloro-4-methoxyphenol to give 2-nitro-3-(2',5'-dichloro-4'-methoxyphenoxy) benzoic acid, the 2-amino, the 2-formamido and finally 7-chloro-8-methoxyphenoxazinyl-1-carboxylic acid.

2,4-dichloro-5-methoxyphenol to give 2-nitro-3-(2',4'-dichloro-5'-methoxyphenoxy) benzoic acid, the 2-amino, the 2-formamido and finally 7-methoxy-8-chlorophenoxazinyl-1-carboxylic acid.

2,4-dichloro-6-carbamylphenol to give 2-nitro-3-(2',4'-dichloro-6-carbamylphenoxy) benzoic acid, the 2-amino, the 2-formamido and finally 6-carbamyl-8-chlorophenoxazinyl-1-carboxylic acid.

2-chloro-4-carbamylphenol to give 2-nitro-3-(2'-chloro-4'-carbamylphenoxy) benzoic acid, the 2-amino, the 2-formamido and finally 8 - carbamylphenoxazinyl-1-carboxylic acid.

2,4-dichloro-6-dimethylcarbamylphenol to give 2-nitro-3-(2',4'-dichloro-6' - dimethylcarbamylphenoxy) benzoic acid, the 2-amino, the 2-formamido and finally 6-dimethylcarbamyl-8-chlorophenoxazinyl-1-carboxylic acid.

2-chloro-6-hexylcarbamylphenol to give 2-nitro-3-(2'-chloro-6' - hexylcarbamylphenoxy) benzoic acid, the 2-amino, the 2-formamido and finally 6 - hexylcarbamylphenoxazinyl-1-carboxylic acid.

Example 18

An excess of diethylaminoethyl chloride (18 g.) is slowly added to a stirred, heated solution of 29.9 g. of 8-trifluoromethylphenoxazinyl-1-carboxylic acid in 250 ml. of isopropanol. After heating at reflux for several hours, the reaction mixture is concentrated and cooled to give diethylaminoethyl 8 - trifluoromethylphenothiazinyl-1-carboxylate hydrochloride. This compound in ether-ethyl acetate is neutralized with carbonate solution to give the free base which is converted into other salts by reaction with excess amounts of the desired acid.

Using 8-chlorophenoxazinyl-1-carboxylic acid and N-methylpiperazinylpropyl chloride the N-methylpiperazinylpropyl ester monohydrochloride is obtained.

Example 19

A mixture of 30 g. of 8-trifluoromethylphenoxazinyl-1-carboxylic acid in 75 ml. of benzene, 30 ml. of dimethylformamide and 10 ml. of phosphorus trichloride is heated at reflux for several hours. The solvents are removed in vacuo to give crude 8 - trifluoromethylphenoxazinyl-1-carbonyl chloride. This material is taken up in ether solution.

An aliquot of the ether solution containing 1 g. of the carbonyl chloride is reacted with an excess of ammonia to separate the 1-carbamyl derivative.

An aliquot containing 1 g. of the carbonyl chloride is reacted with an excess of stearyl alcohol in ether. Evaporation gives the stearyl ester.

An aliquot containing 1 g. of the carbonyl chloride is reacted with aniline to give the N-phenylcarbamyl compound.

An aliquot containing 1 g. of the carbonyl chloride is reacted with an excess of diethylaminoethylamine to give the N-diethylaminoethylcarbamyl derivative. This compound is reacted with an excess of sulfuric acid to give the sulfate salt, heated with ethyl iodide to give the ethiodide.

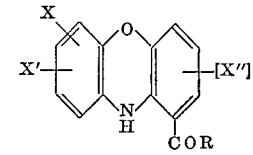
An aliquot containing 1 g. of the carbonyl chloride is reacted with an excess of ethanol to give the ethyl ester.

An aliquot containing 1 g. of the carbonyl chloride is reacted with dibutylamine to give the N,N-dibutyl carbamyl derivative.

Substituting 8-chlorophenoxazinyl-1-carboxylic acid in the reaction with phosphorus trichloride gives 8-chlorophenoxazinyl-1-carbonyl chloride. Thionyl chloride can also be used.

What is claimed is:

1. A compound having the formula:



in which:

X and X' are trifluoromethyl, halo, trifluoromethoxy, methoxy, ethoxy, trifluoromethylthio, sulfamyl, N-methylsulfamyl, N,N-dimethylsulfamyl, methylthio, methylsulfoxy, trifluoromethylsulfoxy, methyl, ethyl, carbamyl, N-methylcarbamyl, N,N-dimethylcarbamyl, methylsulfonyl, trifluoromethylsulfonyl or hydrogen, at least one of X and X' being a substituent other than hydrogen;

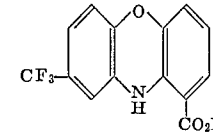
R is hydroxy, alkoxy of 1–18 carbon atoms, dialkylaminoalkoxy or —NR_1R_2; and

R_1 and R_2 are hydrogen, lower alkyl, phenyl or dialkylaminoalkyl.

2. A compound of claim 1 in which X' is hydrogen and X is trifluoromethyl.

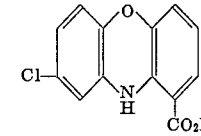
3. A compound of claim 1 in which X' is hydrogen, R is hydroxy and X is trifluoromethyl.

4. A compound of claim 1 in which the formula is:



with its alkali metal and ammonium salts.

5. A compound of claim 1 in which the formula is:



with its alkali metal and ammonium salts.

6. A compound of claim 1 in which R is dialkylaminoalkoxy together with its salts with nontoxic acids.

7. A compound of claim 1 in which R is dialkylaminoalkylamino together with its salts with nontoxic acids.

8. A compound of claim 1 in which X' is hydrogen and X is chloro or trifluoromethyl in the 7, 8 or 9 position.

9. A compound of claim 1 in which X' is hydrogen, R is hydroxy and X is chloro or trifluoromethyl in the 7, 8 or 9 position.

References Cited

UNITED STATES PATENTS

1,551,147	8/1925	Green et al.	260—244
1,766,403	6/1930	Schulemann et al.	260—244
2,576,106	11/1951	Cusic	260—244
2,676,971	4/1954	Cusic	260—244
2,687,414	8/1954	Cusic	260—244

OTHER REFERENCES

Predvoditeleva et al.: "Zhur. Ob. Khim." vol. 30, pp. 1893–7 (1960).

Cauquill et al.: "Bull. Chem. Soc. France," 1960, pp. 1049–1066.

Cauquil et al.: "Comptes Rendus," vol. 243, pp. 590–93 (1956).

Sen et al.: Indian J. of Chemistry, vol. 34, pp. 877–81 (1957).

Sen et al.: Indian J. of Chemistry, vol. 35, pp. 202–204 (1958).

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260—243, 519, 520, 544; 424—248