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4-AMINO-2-SULFAMYLBENZOIC ACID ESTERS

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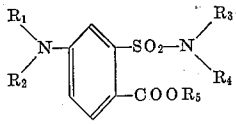
This invention relates to new esters of 4-amino-2-sulfamylbenzoic acids which have useful pharmacodynamic activity.

More specifically, the compounds of this invention have anticonvulsant, muscle relaxant and central nervous system depressant activity. Furthermore, these compounds have psychopharmacological or psychotrophic activity. The anticonvulsant activity of these compounds is especially pronounced.

The novel 4-amino-2-sulfamylbenzoic acid esters of this invention are represented by the following structural formula:

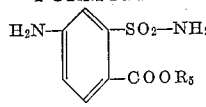
FORMULA I



when R_1, R_2, R_3 and R_4 represent hydrogen or lower alkyl groups having 1 to 6, preferably 1 to 3, carbon atoms; and R_5 represents a branched alkyl group having 3 to 5 carbon atoms, allyl, methallyl, propargyl, cyclopentyl, cyclohexyl and phenyl.

Advantageous compounds of this invention are represented by the following structural formula:

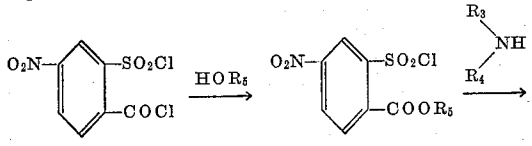
FORMULA II

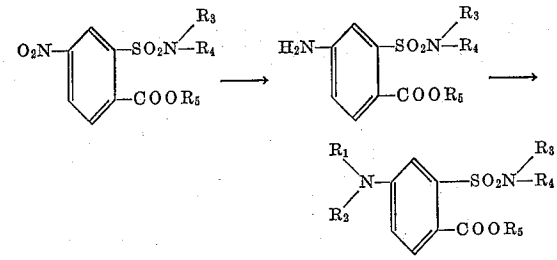


when R_5 represents a branched alkyl group having 3 to 5 carbon atoms. A particularly advantageous and preferred compound of this invention is isopropyl 4-amino-2-sulfamylbenzoate and its nontoxic acid addition salts.

This invention also includes pharmaceutically acceptable salts of the above defined bases formed with nontoxic organic and inorganic acids. Such salts are easily prepared by methods known to the art. The base is reacted with either the calculated amount of organic or inorganic acid in aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling or an excess of the acid in aqueous immiscible solvent, such as ethyl ether or chloroform, with the desired salt separating directly. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic and theophyllineacetic acids as well as with the 8-halotheophyllines, for example, 8-chloro theophylline and 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Of course, these salts also may be prepared by the classical method of double decomposition of appropriate salts which is well-known to the art.

The compounds of this invention are prepared according to the following synthetic procedure:





when R_1, R_2, R_3, R_4 and R_5 are as previously defined.

The known starting material, 4-nitro-2-chloro-sulfonylbenzoyl chloride, is esterified by heating with an excess of the appropriate alcohol at from about 45 to about 65° C. for a short period of time, such as about 30 to 60 minutes. The excess alcohol is removed by evaporation and the residual ester is dissolved in an inert organic solvent such as, for example, ethyl ether, toluene, chloroform or benzene. This solution is added to an organic solvent, preferably ethyl ether, containing an excess of an amine of the formula

where R_3 and R_4 are hydrogen or lower alkyl having 1 to 6 carbon atoms. The resulting solution is filtered and evaporated to give the 4-nitro-2-sulfamylbenzoic acid ester.

Reduction of the 4-nitro-2-sulfamylbenzoic acid ester to the corresponding amino ester is accomplished either by catalytic hydrogenation or chemical reduction. Where catalytic hydrogenation is employed, the nitro ester, in an inert organic solvent such as ethyl acetate, is reduced using a catalyst such as platinum or palladium oxide or, preferably, palladium-on-charcoal at about 40 to 60 p.s.i. for about 30 to 60 minutes at room temperature.

With respect to chemical reduction which is preferred when the ester group is unsaturated, for example, allyl, methallyl or propargyl, the nitro ester is reacted with a chemical reducing agent, for example, with the preferred sodium hydrosulfite in an alkaline solution, such as in a tertiary base, for instance, pyridine.

Mono- and dialkylation of the 4-amino ester is accomplished by refluxing the ester with one or two molar equivalents of a reactive alkyl ester such as the preferred alkyl halides, for example, alkyl chloride, bromide or iodide. Advantageously, the reaction is carried out in an inert organic solvent, such as benzene or toluene, in which at least one of the reactants must be soluble. When a 4-dialkylamino ester is desired, it is advantageous to use an amount of alkyl halide in excess of two molar equivalents.

Dimethylation is conveniently carried out by heating the 4-amino ester at reflux with formic acid and formaldehyde. The 4-dimethylamino ester is conveniently separated from the reaction mixture as its hydrochloride salt.

The following examples are not limiting, but are illustrative of compounds of this invention and will serve to make fully apparent all of the compounds embraced by the general formula given above.

Example 1

A mixture of 3.0 g. of 4-nitro-2-chlorosulfonylbenzoyl chloride and 25 ml. of isopropanol is heated at 50–60° C. for 30 minutes. After cooling, 1 ml. of water is added. The water and excess alcohol are removed by evaporation in vacuo leaving isopropyl 4-nitro-2-chlorosulfonylbenzoate as the residue. The ester is dissolved in 75 ml. of ether and added to 25 ml. of ether which has been saturated with ammonia. The precipitate which forms is

removed by filtration. The filtrate is stripped of ammonia in vacuo, washed with water, dried over anhydrous sodium sulfate and stripped of ether to give, as the residue, isopropyl 4-nitro-2-sulfamylbenzoate, M.P. 128–130° C.

A solution of 10.0 g. of isopropyl 4-nitro-2-sulfamylbenzoate in 150 ml. of ethyl acetate is hydrogenated for 40 minutes at room temperature under about 50 pounds of hydrogen pressure using 1.0 g. of 10% palladium-on-charcoal. The mixture is filtered and the solvent is removed by evaporation in vacuo. The residue is recrystallized from absolute ethanol to give isopropyl 4-amino-2-sulfamylbenzoate, M.P. 120–121° C.

An ether solution of 1.0 g. of the free base is treated with an excess of hydrochloric acid in ethanol. Concentration and cooling yields crystals of isopropyl 4-amino-2-sulfamylbenzoate hydrochloride.

Example 2

A mixture of 4.0 g. of 4-nitro-2-chlorosulfonylbenzoyl chloride and 35 ml. of tertiary butyl alcohol is heated at 60° C. for 40 minutes. The excess alcohol is removed in vacuo and the residue, t-butyl 4-nitro-2-chlorosulfonylbenzoate is dissolved in 100 ml. of ether. This ether solution is added to 30 ml. of a saturated solution of ammonia in ether. The mixture is filtered and excess ammonia is removed in vacuo from the filtrate. The ethereal filtrate is washed with water, dried and stripped of ether to give, as the residue, t-butyl 4-nitro-2-sulfamylbenzoate. Hydrogenation of this nitro ester using palladium-on-charcoal, as outlined in Example 1, gives t-butyl 4-amino-2-sulfamylbenzoate.

The free base (1.0 g.) is dissolved in 100 ml. of ethyl acetate and treated with excess maleic acid to give the maleate salt.

Example 3

4-nitro-2-chlorosulfonylbenzoyl chloride (5.0 g.) and 50 ml. of allyl alcohol are heated at 65° C. for 45 minutes. The excess alcohol is evaporated in vacuo, leaving allyl 4-nitro-2-chlorosulfonylbenzoate as the residue. This ester is dissolved in 100 ml. of benzene and added to 40 ml. of ether saturated with ammonia. The resulting mixture is filtered, stripped of excess ammonia in vacuo, washed with water, dried over anhydrous magnesium sulfate and stripped of solvent to give, as the residue, allyl 4-nitro-2-sulfamylbenzoate.

One gram of this nitro ester is dissolved in 4.5 ml. pyridine, giving a deep red solution. To this is added a solution of 2.7 g. of sodium hydrosulfite in 8 ml. of water. The heterogeneous solution is refluxed with vigorous stirring for two hours. The organic layer is diluted with 25 ml. of water and extracted with benzene, dried and the solvents removed in vacuo, leaving allyl 4-amino-2-sulfamylbenzoate as a pale yellow oil.

The free base, in ether solution, is treated with one molar equivalent of hydrogen bromide in ethanol solution, concentration and cooling yields the hydrobromide salt.

Example 4

A mixture of 3.0 g. of 4-nitro-2-chlorosulfonylbenzoyl chloride and 30 ml. of propargyl alcohol is heated at 50–60° C. for 40 minutes. The excess alcohol is evaporated in vacuo to give propargyl 4-nitro-2-chlorosulfonylbenzoate as the residue. This ester is treated with ammonia, as described in Example 1, to obtain propargyl 4-nitro-2-sulfamylbenzoate.

Reduction of this 4-nitro ester with sodium hydrosulfite as in Example 3 gives propargyl 4-amino-2-sulfamylbenzoate.

Example 5

Methallyl alcohol (50 ml.) and 4-nitro-2-chlorosulfonylbenzoate (4.0 g.) are heated at 55° C. for 50 minutes. The excess alcohol is evaporated in vacuo to leave methallyl 4-nitro-2-chlorosulfonylbenzoate as the residue. The ester is dissolved in 100 ml. of benzene and the resulting solution is added to 30 ml. of ether saturated with ammonia. Filtration, evaporation of excess ammonia, washing with water, drying over anhydrous sodium sulfate, and evaporation of solvent yields methallyl 4-nitro-2-sulfamylbenzoate.

Reduction of this 4-nitro ester with sodium hydrosulfite, as in Example 3, gives methallyl 4-amino-2-sulfamylbenzoate.

Catalytic hydrogenation, as described in Example 1, gives isobutyl 4-amino-2-sulfamylbenzoate.

Example 6

A mixture of 21.3 g. of 4-nitro-2-chlorosulfonylbenzoyl chloride and 35 ml. of cyclopentanol is heated at 60° C. for 45 minutes. The excess alcohol is removed in vacuo, leaving as the residue, cyclopentyl 4-nitro-2-chlorosulfonylbenzoate, M.P. 91–94° C. This ester is dissolved in 100 ml. of benzene and added to 50 ml. of ether saturated with ammonia. The precipitate is filtered off. The filtrate is stripped of ammonia in vacuo, washed with water, dried and stripped of solvent. The residue is recrystallized from ethyl acetate-hexane to give cyclopentyl 4-nitro-2-sulfamylbenzoate, M.P. 170–172° C.

Reduction of this 4-nitro ester by hydrogenation using palladium-on-charcoal, as described in Example 1, gives cyclopentyl 4-amino-2-sulfamylbenzoate which, after recrystallization from ethyl acetate-hexane, melts at 127–128° C.

A solution of 1.0 g. of the free base in 100 ml. of acetone is reacted with an excess of citric acid in acetone to yield, upon concentration and cooling, the citrate salt.

Example 7

4-nitro-2-chlorosulfonylbenzoyl chloride (12.0 g.) and phenol (20.0 g.) are heated at 65° C. for one hour. The excess phenol is removed by evaporation in vacuo. The residue, phenyl 4-nitro-2-chlorosulfonylbenzoate, is dissolved in 100 ml. of ether and added to 40 ml. of ether saturated with ammonia. The resulting mixture is filtered, the excess ammonia is evaporated in vacuo, the ethereal solution is washed with water, dried, and stripped of solvent to give phenyl 4-nitro-2-sulfamylbenzoate as the residue.

Ten grams of the nitro ester are dissolved in 150 ml. of ethyl acetate and hydrogenated under 50 pounds of hydrogen pressure for about 30 minutes using 2.0 g. of 10% palladium-on-charcoal catalyst. The resulting mixture is filtered and stripped of solvent. Recrystallization of the residue from absolute ethanol yields phenyl 4-amino-2-sulfamylbenzoate.

The product (1.0 g.) is dissolved in ether and treated with an excess of alcoholic hydrogen chloride to separate the hydrochloride salt.

Example 8

A mixture of 3.0 g. of 4-nitro-2-chlorosulfonylbenzoyl chloride and 25 ml. of 3-pentanol is heated at 50–60° C. for 40 minutes. Evaporation of excess alcohol yields 3-pentyl 4-nitro-2-chlorosulfonylbenzoate. Treatment of this ester with an ether solution saturated with ammonia and isolation of 3-pentyl 4-nitro-2-sulfamylbenzoate are carried out as described in Example 7.

Reduction of this 4-nitro ester by hydrogenation with palladium-on-charcoal catalyst yields 3-pentyl 4-amino-2-sulfamylbenzoate.

Example 9

Cyclohexanol (40 ml.) and 20.0 g. of 4-nitro-2-chlorosulfonylbenzoyl chloride are heated at 55° C. for 45 minutes. Evaporation of the excess cyclohexanol yields cyclohexyl 4-nitro-2-chlorosulfonylbenzoate. This ester is dissolved in 150 ml. of benzene and added to 35 ml. of ether saturated with ammonia. The resulting mixture is filtered, stripped of excess ammonia, washed with water, dried and stripped of solvent. The residue is

recrystallized from ethyl acetate-hexane to give cyclohexyl 4-nitro-2-sulfamylbenzoate.

Hydrogenation of this nitro ester using palladium-on-charcoal as a catalyst gives cyclohexyl 4-amino-2-sulfamylbenzoate.

Example 10

A solution of 15.3 g. of isopropyl 4-nitro-2-chlorosulfonylbenzoate, made as in Example 1, in 010 ml. of ether is added to a saturated solution of methylamine in 25 ml. of ether. The resulting mixture is filtered and the excess methylamine is removed in vacuo. The residue is washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo gives isopropyl 4-nitro-2-(N-methylsulfamyl)-benzoate, M.P. 117–120° C.

Reduction of the nitro compound in ethyl acetate over palladium-on-charcoal catalyst, as in Example 1, gives isopropyl 4-amino-2-(N-methylsulfamyl)-benzoate which, after recrystallization from isopropanol-hexane, melts at 122–123.5° C.

Example 11

To a saturated solution of dimethylamine in 25 ml. of ether is added an ether solution of 15.3 g. of isopropyl 4-nitro-2-chlorosulfonylbenzoate, prepared as in Example 1. The resulting mixture is filtered and the excess dimethylamine is evaporated in vacuo. The ethereal residue is washed with water, dried and stripped of solvent to give isopropyl 4-nitro-2-(N,N--dimethylsulfamyl)-benzoate as the residue. Recrystallization gives crystals melting at 82–84° C.

Hydrogenation of the nitro ester with palladium-on-charcoal catalyst, as in Example 1, gives isopropyl 4-amino-2-(N,N-dimethylsulfamyl)-benzoate, M.P. 148–150° C.

Example 12

To a mixture of 25.8 g. of isopropyl 4-amino-2-sulfamylbenzoate, prepared as in Example 1, and 20.0 g. of 90% formic acid is added 17.0 g. of 37% formaldehyde solution. The resulting solution is heated at reflux for about four hours. An excess of hydrochloric acid is added and the solution concentrated. Crystals of isopropyl 4-dimethylamino-2-sulfamylbenzoate hydrochloride are isolated by filtration.

Example 13

A mixture of 25.8 g. of isopropyl 4-amino-2-sulfamylbenzoate, prepared as in Example 1, and 14.2 g. of methyliodide in benzene is refluxed for two hours. The solvent is removed by evaporation in vacuo. The residue is recrystallized from absolute ethanol to give isopropyl 4-methylamino-2-sulfamylbenzoate hydroiodide.

Example 14

A solution of 15.2 g. of allyl 4-nitro-2-chlorosulfonylbenzoate, made as in Example 3, in 100 ml. of ether is added to a saturated solution of ethylamine in 25 ml. of ether. The resulting mixture is filtered and the excess ethyl amine is removed by evaporation in vacuo. The ethereal residue is washed with water, dried over anhydrous magnesium sulfate and evaporated to give allyl 4-nitro-2-(N-ethylsulfamyl)-benzoate.

This nitro ester is dissolved in pyridine and reduced by refluxing with sodium hydrosulfite. Working up the reaction mixture, as in Example 3, yields allyl 4-amino-2-(N-ethylsulfamyl)-benzoate.

Example 15

A solution of 15.3 g. of isopropyl 4-nitro-2-chlorosulfonylbenzoate, prepared as in Example 1, in 100 ml. of ether is added to 35 ml. of an ether solution saturated with diethylamine. The resulting mixture is filtered; excess diethylamine is evaporated in vacuo. The residue is washed with water, dried over anhydrous magnesium sulfate and stripped of solvent to give isopropyl 4-nitro-2-(N,N-diethylsulfamyl)-benzoate as the residue.

Hydrogenation of the nitro ester with palladium-on-charcoal as catalyst, as in Example 1, gives isopropyl 4-amino-2-(N,N-diethylsulfamyl)-benzoate.

Example 16

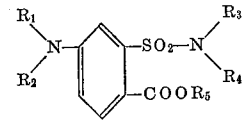
A mixture of 3.1 g. of isopropyl 4-amino-2-(N,N-diethylsulfamyl)-benzoate, prepared as in Example 15, and 2.2 g. of ethylbromide in benzene is refluxed for two hours. The solvent is evaporated in vacuo. The residue is recrystallized from isopropanol to give isopropyl 4-diethylamino-2-(N,N-diethylsulfamyl)-benzoate hydrobromide.

Example 17

A mixture of 2.5 g. of isopropyl 4-amino-2-sulfamylbenzoate, prepared as in Example 1, and 4.0 g. of n-hexylbromide in 100 ml. of benzene is refluxed for three hours. Evaporation of the solvent and recrystallization of the residue from isopropyl alcohol gives isopropyl 4-dihexylamino-2-sulfamylbenzoate hydrobromide.

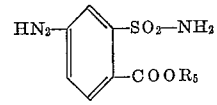
What is claimed is:

1. A chemical compound of the class consisting of a free base and its nontoxic acid addition salts, the free base having the following structural formula:



in which R_1, R_2, R_3, and R_4 are members selected from the group consisting of hydrogen and lower alkyl having from 1 to 6 carbon atoms, and R_5 is a member selected from the group consisting of a branched alkyl group having from 3 to 5 carbon atoms, allyl, methallyl, propargyl, cyclopentyl, cyclohexyl and phenyl.

2. A chemical compound having the basic structural formula:



in which R_5 is a branched alkyl group having from 3 to 5 carbon atoms.

3. Isopropyl 4-amino-2-sulfamylbenzoate.
4. Isopropyl 4-methylamino-2-sulfamylbenzoate.
5. Isopropyl 4-dimethylamino-2-sulfamylbenzoate.
6. Phenyl 4-amino-2-sulfamylbenzoate.
7. Allyl 4-amino-2-sulfamylbenzoate.

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