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2-METATRIFLUOROMETHYLANILINO-PYRIDINE-5-N-ACETYL SULFONAMIDE

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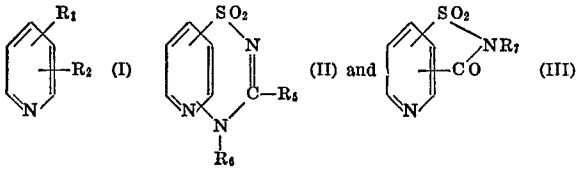
ABSTRACT OF THE DISCLOSURE

Compounds of formulae

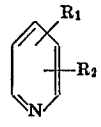


wherein R_1 represents a sulfonic acid, sulfonamido group when R_2 represents a substituted anilino group and R_1 represents in addition to the above-indicated groups, a cyano, carboxy or carboxamido group when R_2 represents a N-lower alkylpiperazino group; R_5 and R_7 represent each a lower alkyl group and R_6 represents hydrogen or a lower alkyl or aryl group; as well as the pharmaceutically acceptable salts thereof. These compounds have valuable anti-inflammatory and anti-pyretic properties.

BACKGROUND OF THE INVENTION

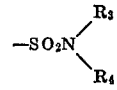
The present invention relates to new derivatives of pyridine having valuable pharmacological properties.

According to one feature of the present invention there are provided compounds of formula



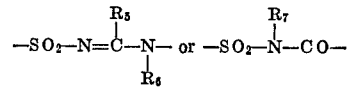
(I)

wherein R_1 in the 3- or 5-position of the pyridine nucleus represents a sulfonic acid group, the esters and salts thereof, a primary, secondary or tertiary sulfonamido or sulfamyl group which may be substituted, a group of formula

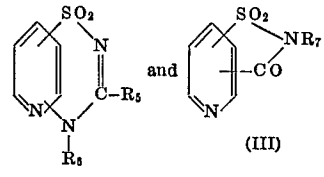


in which R_3 and R_4 form together with the nitrogen atom to which they are attached a heterocyclic ring which may contain another hetero-atom and may also be substituted, when R_2 in the 2- or 4-position of the pyridine nucleus represents an anilino group which is substituted; or R_1, in the 3- or 5-position, in addition to the meanings given hereabove, may also represent a cyano, a carboxy group, the esters and salts thereof, a primary, secondary or tertiary carboxamide or carbamyl group when R_2 in the 2- or 4-position represents a piperazinyl group which may be substituted; or R_1 and R_2 when attached to adjacent carbon atoms of the pyridine nucleus may form together

with one another and said adjacent carbon atoms a group of formulae



the ends of which are attached to said adjacent carbon atoms and wherein R_5 and R_7 represent each a lower alkyl group whereas R_6 represents hydrogen or a lower alkyl or an aryl group which may be substituted said compounds being thus respectively of formulae:



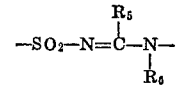
(II) (III)

and the pharmaceutically acceptable salts of the compounds of formulae I, II and III.

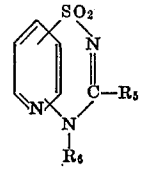
In general formula I, R_1 advantageously represents a sulfonic acid or sulfonate, sulfonamido or sulfamyl, mono- and di-lower alkylsulfonamido, arylsulfonamido which latter may be substituted with one or two lower alkyl, halogeno, nitro or trifluoromethyl group, R_1 may also represents a morpholino sulfone, lower alkylpiperazinylsulfone group, whereas R_2 represents a meta-trifluoromethylanilino group when R_1 has any one of the above indicated meanings.

Also preferably R_2 represents a lower alkyl-piperazinyl group and R_1 not only has the meanings indicated hereabove, but also represents a cyano, carboxy, carboxylate, carboxamido or carbamyl, mono- and di-lower alkylcarboxamido.

Preferred compounds of formula II are those wherein R_1 attached to the carbon atoms in the 3-position of the pyridine nucleus and R_2 attached to the carbon atom in the 2- or 4-position of said pyridine nucleus form together with one another and with said carbon atoms a group of formula



the ends of which are attached to said carbon atoms and wherein R_5 represents a lower alkyl group whereas R_6 represents a meta-trifluoromethylphenyl group, said compound being thus of formula

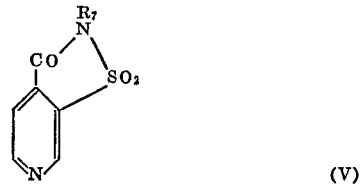


(IV)

Preferred compounds of formula III are those wherein R_1 attached to the carbon atom in the 5-position of the pyridine nucleus and R_2 attached in the 4-position of said

pyridine nucleus form together with one another and with said carbon atoms a group of formula

the ends of which are attached to said carbon atoms, said compounds being thus of formula



(V)

Among the compounds of formulae I, II and III and their acid addition salts according to the present invention the following are preferred on account of their especially favourable pharmacological properties:

2-meta-trifluoromethylanilino-pyridine-3-sulfonic acid;
2-meta-trifluoromethylanilino-pyridine-3-sulfonamide;
2-meta-trifluoromethylanilino-pyridine-3-monomethylsulfonamide;
2-meta-trifluoromethylanilino-pyridine-3-dimethylsulfonamide;
2-meta-trifluoromethylanilino-pyridine-3-morpholinosulfone;
2-meta-trifluoromethylanilino-pyridine-3-N-methylpiperazinyl-sulfone;
2-meta-trifluoromethylanilino-pyridine-3-metachlorophenyl sulfonamide;
2-meta-trifluoromethylanilino-pyridine-3-N-acetylsulfonamide;
3-methyl-4-(3'-trifluoromethyl)phenyl-4-H-pyrido-2,3-e-thia-2-4-diazine-1,1-dioxide;
2-meta-trifluoromethylanilino-pyridine-5-sulfonic acid;
2-meta-trifluoromethylanilino-pyridine-5-sulfonamide;
2-meta-trifluoromethylanilino-pyridine-5-monomethylsulfonamide;
2-meta-trifluoromethylanilino-pyridine-5-dimethylsulfonamide;
2-meta-trifluoromethylanilino-pyridine-5-hydroxyethylsulfonamide;
2-meta-trifluoromethylanilino-pyridine-5-morpholino sulfone;
2-meta-trifluoromethylanilino-pyridine-5-N-methylpiperazinyl sulfone;
2-meta-trifluoromethylanilino-pyridine-5-(2'-methyl-3'-chlorophenyl)sulfonamide;
2-meta-trifluoromethylanilino-pyridine-5-N-acetylsulfonamide;
4-meta-trifluoromethylanilino-pyridine-5-sulfonic acid;
4-meta-trifluoromethylanilino-pyridine-5-sulfonamide;
4-meta-trifluoromethylanilino-pyridine-5-monomethylsulfonamide;
4-meta-trifluoromethylanilino-pyridine-5-morpholino sulfone;
4-meta-trifluoromethylanilino-pyridine-5-N-methylpiperazinyl sulfone;
4-meta-trifluoromethylanilino-pyridine-5-metachlorophenyl sulfonamide;
4-meta-trifluoromethylanilino-pyridine-5-N-acetylsulfonamide;
4-carboxypyridine-5-sulfonimide;
2-(4'-methyl-1'-piperazinyl)-pyridine-4-sulfonamide;

2-(4'-methyl-1'-piperazinyl)-pyridine-3-methylsulfonamide;
2-(4'-methyl-1'-piperazinyl)-pyridine-3-dimethylsulfonamide;
2-(4'-methyl-1'-piperazinyl)-pyridine-3-ethylsulfonamide;
2-(4'-methyl-1'-piperazinyl)-pyridine-3-diethylsulfonamide dihydrochloride;
2-(4'-methyl-1'-piperazinyl)-pyridine-3-isopropylsulfonamide;
2-(4'-methyl-1'-piperazinyl)-pyridine-3-(4'-methyl-1'-piperazinyl)-sulfonamide dihydrochloride;
2-(4'-methyl-1'-piperazinyl)-pyridine-5-sulfonic acid;
2-(4'-methyl-1'-piperazinyl)-pyridine-5-sulfonamide;
2-(4'-methyl-1'-piperazinyl)-pyridine-5-methylsulfonamide;
2-(4'-methyl-1'-piperazinyl)-pyridine-5-dimethylsulfonamide;
2-(4'-methyl-1'-piperazinyl)-pyridine-5-ethylsulfonamide;
2-(4'-methyl-1'-piperazinyl)-pyridine-5-diethylsulfonamide;
2-(4'-methyl-1'-piperazinyl)-pyridine-5-isopropylsulfonamide;
2-(4'-methyl-1'-piperazinyl)-3-cyano-pyridine hydrochloride;
2-(4'-methyl-1'-piperazinyl)-nicotinic acid;
2-(4'-methyl-1'-piperazinyl)-pyridine-3-diethylcarboxamide and the hydrochloride thereof;
2-(4'-methyl-1'-piperazinyl)-pyridine-5-diethylcarboxamide and the hydrochloride thereof.

Among the acid addition salts of the compounds of formulae I, II and III, the hydrochlorides are preferred.

The compounds according to formulae I, II and III, have valuable anti-inflammatory and anti-pyretic properties as shown by the following pharmacological tests.

1°—Inducted rat paw oedema

The drugs to be tested are given as freshly prepared solutions or suspensions by oral route one hour before injecting the paw with the inflammatory agent.

A phlogogenous or inflammatory agent (such as kaolin, ovalbumin, carrageenan) either in aqueous solution or suspension is then injected into the plantar tissue of the right hind paw of each rat, the left paw remaining untreated and serving as control. Each animal receives for example 0.05 ml. of an aqueous solution containing 1% of carrageenan and 0.9% of sodium chloride.

4 hours after injection, the importance of swelling is determined by plethysmography and is expressed as a percent of the value of the control paw.

The anti-inflammatory effect expressed as a percent of inhibition is obtained by comparison between rats treated with the anti-inflammatory agent and a control group of rats.

2°—Freund adjuvant induced arthritis in rats

0.1 ml. of Freund adjuvant (suspension of *Mycobacterium butyricum* in paraffin oil) is injected into the plantar tissue of the right hind paw of each rat.

The anti-inflammatory treatment starts 2 days after injection of said adjuvant and is continued for 5 days. Every day, the volume of the treated paw is determined by plethysmorgraphy and the results are expressed as percentages of inhibition with respect to control animals.

3°—Anti-pretic action

Hyperthermia is induced in rats by intraperitoneal injection of a 5% aqueous suspension of barm, the day before the treatment with anti-pyretic agent. The fever is measured by means of a rectal thermocouple and the fall in bodily temperature of the treated animals is expressed with reference to the control animals.

The results of the above tests are indicated in the following table I:

TABLE I

	Anti-inflammatory action, percent				
	Acute oedema (Test 1) induced by—			Arthritis with adjuvant (Test 2), percent	Anti-pyretic action, (Test 3), degrees
	Carrageenan	Kaolin	Ovalbumin		
Compound of Example:					
20	46	60	30	38	−3.5
1	13	26	24	26	−1.8
11	51	45	40	28	−2.5
19	49	50	35	32	−2.7
26	32	25	30	18	−3.5
2	43	38	23	20	−3.0
13	25	28	17	17	−3.5
10	28	32	15	12	−3.0
12	22	10	24	13	−3.5
29	27	30	25	18	−5.5
Phenylbutazone	41	52	0	20	−1
Methiazinic acid	46	50	12	12	−3
Acetosalicylic acid	0	24	5	13	−1.5
Flufenamic acid	34	27	0	18	−1.2
Niflumic acid	32	17	0	22	−1.5

N.B.:
In Test 1, 100 mg./kg. of anti-inflammatory agent are administered by oral route.
The results of Tests 1 and 2 are percentages of inhibition.

According to a further feature of the present invention we provide pharmaceutical compositions comprising as active ingredient, at least one compound according to the present invention, together with a pharmaceutical carrier or excipient. The compositions are generally intended for peroral rectal or parenteral administration and also for external use. Pharmaceutical compositions for oral administration may, for example, be in the form of dosage units such as tablets, dragees or capsules in which at least one of the compounds according to the invention is mixed with a solid pharmaceutical carrier or excipient.

The compositions according to the present invention can also be used in the form of liquid preparations for oral administration especially syrups, elixirs, aqueous dispersions or solutions.

The compositions according to the present invention can also be in the form of solutions for parenteral administration. Solutions or suspensions for injections can be prepared by using, for example, distilled water in which at least one compound employed as active ingredient is dissolved or suspended, if desired, in the presence of a solubilizing agent.

The compositions according to the present invention may also be formulated for rectal administration, for example, the active ingredient in a suppository base.

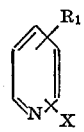
The anti-inflammatory compositions according to this invention may also be applied for external use, for example, the active ingredient in an ointment base.

The compounds employed as active ingredients in the compositions according to the invention can be administered in varying doses depending on the particular compound being used. The condition of the patient, and the route of administration.

In general, however, the compounds can be administered orally or rectally in doses of from 50 to 1000 mg. to be taken one to four times per day, or parenterally in a single dose of 20 to 500 mg. per day.

The compounds of this invention may be prepared according to the following processes which constitute further features of the present invention. Thus according to the present invention there are provided:

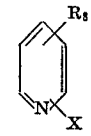
(a) A process for preparing compounds of formula I (wherein R_1 in the 3- or 5-position is as defined hereabove and R_2 in the 2- or 4-position represent a piperazinyl or substituted piperazinyl group) which comprises reacting a compound of formula



(VI)

(wherein R_1 in the 3- or 5-position is as defined hereabove and X in the 2- or 4-position represents a halogen group) with piperazine or substituted piperazine;

(b) A process for preparing compounds of formula I (wherein R_1 in the 3- or 5-position is as defined hereabove except the following groups: cyano, carboxy, carboxylate esters and salts; primary, secondary or tertiary carboxamide or carbamyl; and R_2 in the 2- or 4-position represents a substituted anilino group, which comprises reacting a compound of formula

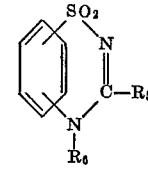


(VII)

(wherein R_8 in the 3- or 5-position has all the meanings of R_1 given hereabove except the following groups: cyano, carboxy, carboxylate esters and salts, primary, secondary or tertiary carboxamido or carbamyl; and X in the 2- or 4-position is as defined hereabove) with substituted aniline;

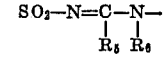
(c) A process for preparing compounds of formula I (wherein R_1 represents a primary, secondary or tertiary sulfamyl or sulfonamido group) which comprises transforming a compound of formula I (wherein R_1 represents a sulfonic acid group in the 3- or 5-position and R_2 represents a substituted anilino group) into the corresponding sulfochloride and reacting the latter with ammonia, a primary or secondary aliphatic or aromatic amine which may be substituted or a nitrogenous heterocyclic compound which may contain another hetero-atom and may also be substituted;

(d) A process for preparing compounds of formula



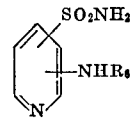
(II)

(wherein the ends of the group



are linked to adjacent carbon atoms of the pyridine nucleus, R_5 represents a lower alkyl group and R_6 represents hydrogen, a lower alkyl or an aryl group which may

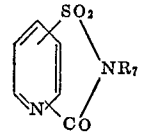
be substituted) which comprises cyclizing a compound of formula



(VIII)

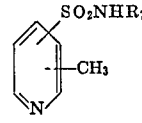
(wherein the substituents are attached to adjacent carbon atoms of the pyridine nucleus and R_6 is as defined hereabove) with a cyclizing agent of formula $(R_5CO)_2O$ (wherein R_5 is as defined hereabove);

(e) A process for preparing compounds of formula



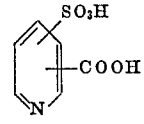
(III)

(wherein the ends of group $—SO_2—NR_7—CO—$ are linked to adjacent carbon atoms of the pyridine nucleus, R_7 represents a lower alkyl group), which comprises either oxydizing and cyclizing a compound of formula



(IX)

(wherein the substituents are attached to adjacent carbon atoms of the pyridine nucleus, and R_7 is as defined hereabove) or cyclizing a compound of formula



(X)

(wherein the substituents are attached to adjacent carbon atoms of the pyridine nucleus) with a compound of formula NH_2R_7 (wherein R_7 is as defined hereabove).

In each of the above processes, whenever there is obtained a compound of formula I wherein R_1 represents a primary or secondary sulfonamido or carboxamido group, said compound may be acylated and whenever there is obtained a compound of formula I wherein R_1 represents a cyano group, said compound may be hydrolyzed to give a compound of formula I wherein R_1 is either carbamyl or carboxy depending on the extent of hydrolysis.

The compounds of this invention may be converted, where possible, into their acid addition salts, preferably hydrochlorides, by conventional methods.

Still a further feature of the invention is provided by some new compounds of formula VI (wherein R_1 in the 3-position has any of the meanings indicated hereabove except the following groups: cyano, carboxy and carboxylate, whereas X represents a halogeno group in the 2- or 4-position).

The preferred compounds are

2-chloropyridine-3-sulfonamide
4-chloropyridine-5-sulfonic acid
2-chloropyridine-3-methylsulfonamide
2-chloropyridine-3-dimethylsulfonamide
2-chloropyridine-3-ethylsulfonamide
2-chloropyridine-3-diethylsulfonamide
2-chloropyridine-3-isopropylsulfonamide
2-chloropyridine-3-diethylcarboxamide

The compounds of formula VI wherein R_1 represents a sulfonamido group may be obtained from the corresponding compounds wherein R_1 represents a sulfonic acid group by transforming the latter into a sulfochloride and reacting the latter with ammonia, a primary or secondary amine.

The compounds of formula VI wherein R_1 represents a carboxamido group may be obtained from the corresponding non-halogenated compounds, by halogenating the latter.

Other compounds of formula VI wherein R_1 is a sulfonic acid group in the 5-position may be obtained from the corresponding hydroxy sulfonic acids by substituting the hydroxy group thereof with a halogen atom.

DETAILED DESCRIPTION OF THE INVENTION

For a better understanding of the present invention, the following examples are given by way of illustration only:

EXAMPLE 1

Preparation of 2-meta-trifluoromethylanilino-pyridine-3-sulfonic acid

0.1 mole of 2-chloropyridine-3-sulfonic acid, 0.2 mole of meta-trifluoromethylaniline and 500 mg. of copper powder are heated for 3 hours at 130° C.

The reaction product is triturated together with acetone. There remains an insoluble matter which is separated from the acetone. The insoluble matter which consists of crude 2-meta-trifluoromethylanilino-pyridine-3-sulfonic acid, together with copper is mixed with a mixture (60:40) of water and alcohol and active carbon and the resulting mixture is caused to boil. Filtration gives a limpid solution which is cooled and may be evaporated for crystallizing the desired sulfonic acid. Yield: 60–70%. Melting point: 278–279° C.

Elementary analysis:

Calculated: C 45.28%; H 2.85%; N 8.80%; S 10.07%
Found: C 45.41%; H 2.93%; N 8.74%; S 9.89%

EXAMPLE 2

Preparation of 2-meta-trifluoromethylanilino-pyridine-3-sulfonamide

The starting material 2-chloropyridine-3-sulfonamide is first prepared as follows:

Method (a): The following mixture is heated for 30 minutes at 130–140° C.:

10 g. of 2-chloropyridine-3-sulfonic acid, 15 g. of PCl_5 and a little $OPCl_3$.

The phosphorus oxychloride is distilled off in vacuo and the residue is extracted with 250 ml. of anhydrous benzene. A stream of gaseous ammonia is passed or bubbled through the solution first for 30 minutes in the cold state and then for 1.5 hour with reflux heating. Upon cooling, a precipitate is formed. The latter is collected, dried and completely extracted with absolute ethanol. Evaporation of the ethanol leaves a residue which is dried and crushed and then extracted with ether to give the desired 2-chloropyridine-3-sulfonamide. Yield: 70–80%.

Method (b): Alternately, after distillation of the $OPCl_3$, the residue instead of being extracted with benzene, is poured onto 200 g. of crushed ice. The mixture is stirred vigorously and 200 ml. of ether are added after a few minutes. Vigorous stirring is continued and at the same time, the reaction mixture is neutralized with dry $NaHCO_3$. The mixture is extracted two times with 300 ml. of ether. The ethereal solution is dried and the solvent evaporated in vacuo. The residue is extracted with 30 ml. of acetone. The new solution is poured little by little and under vigorous stirring into 200 ml. of concentrated ammonia. After 0.5 hour, the solution is evaporated under reduced pressure to a little volume. The desired 2-chloropyridine-3-sulfonamide crystallizes. Yield: 70–80%. The desired product may be recrystallized from a mixture of benzene and ethanol, m.p. 187–188° C.

Elementary analysis:

Calculated: C 31.17%; H 2.62%; N 14.54%; S 16.64%; Cl 18.40%
Found: C 31.06%; H 2.32%; N 14.89; S 16.21%; Cl 18.81%

Using 2-chloropyridine-3-sulfonamide prepared as described hereabove, the end product 2-meta-trifluoromethylanilino pyridine 3-sulfonamide is now prepared as follows:

The following mixture is heated for 4 hours at about 140–150° C.: 0.1 mole of 2-chloropyridine-3-sulfonamide, 0.2 mole of meta-trifluoromethylaniline and 500 mg. of copper powder.

The reaction mass is cooled and triturated together with acetone. Thereafter, water is added until precipitation stops. An insoluble precipitate is thus obtained, collected and treated with boiling 6N solution of HCl in the presence of active carbon. After filtration and evaporation to dryness, the residue is dissolved in water and ammonia is added thereto up to neutrality. A violaceous product is obtained, purified by repeated crystallizations from a mixture (2:1) of water and ethanol in the presence of active carbon. The desired end product is isolated as white crystals. Yield: 60–70%.

The desired end product can also be obtained as follows: 10 g. of 2-meta-trifluoromethylanilino-pyridine-3-sulfonic acid are heated with 10 g. of PCl_5 and a little $OPCl_3$ for 1 hour at 130–140° C.

The $OPCl_3$ is distilled off in vacuo and the residue is extracted with 30 ml. of acetone, poured dropwise and with good stirring into 200 ml. of concentrated ammonia. After 0.5 hour of stirring at ambient tempertaure, the solution is evaporated to a little volume. The collected product is recrystallized from a mixture of water and alcohol (2:1) in the presence of active carbon with a yield of 70–80%, m.p. 183° C.

Elementary analysis:

Calculated: C 45.43%; H 3.18%; N 10.11%; S 13.24%

Found: C 45.33%; H 2.85%; N 10.47%; S 13.15%

EXAMPLE 3

Preparation of 2-meta-trifluoromethylanilino-pyridine-3-monomethylsulfonamide

10 g. of 2-meta-trifluoromethylanilino-pyridine-3-sulfonic acid are heated with 10 g. of PCl_5 and a little $OPCl_3$ for 1 hour at 130–140° C. The $OPCl_3$ is distilled off in vacuo, the residue is extracted with 30 ml. of acetone and is poured dropwise and with good stirring into a large excess of aqueous solution (30%) of monomethylamine (NH_2CH_3). After 0.5 hour of stirring at ambient temperature, the acetone is evaporated and the excess of monomethylamine as well. The desired sulfonamide precipitates. It is collected, washed with water, and absolute ethanol and benzene are added thereto. The solvents are partly distilled off to remove a little residual amount of water. Petroleum ether, boiling point 100–140° C., is then added. The mixture is further evaporated and the desired sulfonamide precipitates as white needles with a yield of 60–70%, m.p. 119.5–120° C.

Elementary analysis:

Calculated. C 47.13%; H 3.65% N 12.68%; S 9.68%

Found: C 46.89%; H 3.70%; N 12.42%; S 9.50%

EXAMPLE 4

Preparation of 2-meta-trifluoromethylanilino-pyridine-3-dimethylsulfonamide

The method of Example 3 is applied except that a solution of dimethylamine ($NH(CH_3)_2$ is used. After distillation of the excess of amine and acetone, an oil precipitate separates and crystallizes at rest. It is the desired sulfonamide which may be recrystallized from a mixture (1:2) of water and ethanol. Yield: 60–70%; m.p. 89–90° C.

Elementary analysis:

Calculated: C 48.69%; H 4.09%; N 12.17%; S 9.28%

Found: C 48.73%; H 3.97%; N 12.32%; S 9.11%

EXAMPLE 5

Preparation of 2-meta-trifluoromethylanilino-pyridine-3-morpholino-sulfone

The method of Example 3 is applied except that an excess of 30% aqueous solution of morpholine is used. After evaporation of the acetone, the desired sulfone separates as an oily precipitate which is collected, dehydrated by evaporation with a mixture of ethanol and benzene and crystallized from petroleum ether (b.p.: 100–140° C.). Yield: 60–70%; m.p. 122–123° C.

Elementary analysis:

Calculated: C 49.61%; H 4.16%; N 10.85%; S 8.28%

Found: C 49.72%; H 3.95%; N 10.59%; S 8.30%

EXAMPLE 6

Preparation of 2-meta-trifluoromethylanilino-pyridine-3-N-methylpiperazinyl-sulfone

The method of Example 3 is applied except that a solution of N-methylpiperazine is used. An oily precipitate is obtained as in said Example. It is redissolved in slightly acid medium comprising a great volume of water. (About 4 l. of water are necessary for 10 g. of the desired sulfone). The aqueous solution is heated to 50° C. and alcalinized with NH_4OH. The desired sulfone crystallizes slowly and is advantageously recrystallized from petroleum ether (b.p. 100–140° C.). Yield: 60–70%; m.p. 69° C.

Elementary analysis:

Calculated: C 50.99%; H 4.78%; N 13.99%; S 8.01%

Found: C 50.72%; H 5.02%; N 14.09%; S 8.20%

EXAMPLE 7

Preparation of 2-meta-trifluoromethylanilino-pyridine-3-metachlorophenyl sulfonamide

10 g. of 2-meta-trifluoromethylanilino-pyridine-3-sulfonic acid are transformed into the corresponding sulfochloride as in Example 3. The sulfochloride is separated from the $OPCl_3$ and extracted with 50 ml. of a mixture (50:50) of pyridine and acetone. A solution is thus obtained and poured dropwise and with good stirring into a mixture of 20 g. of metachloraniline and 100 ml. of acetone. The reaction mixture is allowed to react for 1 hour at ambient temperature. The solvent is then distilled off under reduced pressure. The reddish viscous residual liquid is triturated with 5N HCl until crystallization. The crude product is separated, washed with water, dried and recrystallized from petroleum ether (b.p.: 100–140° C.). The desired sulfonamide crystallizes as white crystal with a yield of 40%, m.p.: 106° C.

Elementary analysis:

Calculated: C 50.53%; H 3.06%; N 9.82; S 7.49%; Cl 8.29%

Found: C 50.36%; H 3.25%; N 9.75%; S 7.58%; Cl 8.40%

EXAMPLE 8

Preparation of 2-meta-trifluoromethylanilino-pyridine-3-N-acetylsulfonamide

75 g. of pyridine and 75 g. of acetic anhydride are added to 15 g. of 2-meta-trifluoromethylanilino-pyridine-3-sulfonamide. The mixture is stirred for 12 hours at ambient temperature in a hermetically closed flask and is shaked from time to time. Thereafter, it is poured into 2 liter of 10% NaOH and dissolved at a maximum with slight heating when necessary. The mixture is filtered, the filtrate is neutralized and gives an abundant precipitate. The latter is collected, washed and then treated in the cold state by means of 2 liters of 5% $NaHCO_3$ in water. The mixture is vigorously stirred to dissolve the obtained desired acetylsulfonamide. The

unreacted sulfonamide is separated by filtration and the filtrate is neutralized by means of HCl. The desired 2-meta - trifluoromethylanilino - pyridine-3-n-acetylsulfonamide precipitates and may be recrystallized from a mixture (1:2) of water and ethanol. Yield: 60–70%; m.p. 145° C.

Elementary analysis:

Calculated: C 46.79%; H 3.37%; N 11.69%; S 8.92%

Found: C 46.80%; H 3.52%; N 11.59%; S 9.00%

EXAMPLE 9

Preparation of 3-methyl-4(3'-trifluoromethyl)phenyl-4H-pyrido-2,3-e-thia-2-4-diazine-1,1-dioxide

10 g. of 2-meta-trifluoromethylanilinopyridine-3-sulfonamide are poured little by little into 10 ml. of acetic anhydride at 70–80° C. The mixture is refluxed for 1 hour and then strongly cooled. The desired product crystallizes and may be recrystallized from diluted alcohol. Yield: 60–70%; m.p. 193° C.

Elementary analysis:

Calculated: C 49.27%; H 2.95%; N 12.31%; S 9.39%

Found: C 49.26%; H 2.90%; N 12.49%; S 9.53%

EXAMPLE 10

Preparation of 2-meta-trifluoromethylanilino-pyridine-5-similar; m.p. 255–256° C.

The method of Example 1 is applied, using 2-chloropyridine-5-sulfonic acid as starting material. The yield is similar; m.p. 255–256° C.

similar m.p. ²55–256° C.

Elementary analysis:

Calculated: C 45.28%; H 2.85%; N 8.80; S 10.07%

Found: C 45.11%; H 2.99%; N 8.65%; S 10.21%

EXAMPLE 11

Preparation of 2-meta-trifluoromethylanilino-pyridine-5-sulfonamide

Both methods described in Example 2 may be applied, using respectively 2-chloropyridine-5-sulfonamide and 2-meta-trifluoromethylanilino-pyridine - 5 - sulfonic acid. When applying method (a), the reaction product needs merely to be extracted with acetone, heated for dissolution purposes, filtered and an excess of water added to it. The desired product precipitates and is recrystallized from diluted ethanol. The yield is similar with that of Example 2. m.p. 180° C.

Elementary analysis:

Calculated: C 45.43%; H 3.18%; N 10.11%; S 13.24%

Found: C 45.64%; H 3.30%; N 10.00%; S 13.31%

EXAMPLE 12

Preparation of 2-meta-trifluoromethylanilino-pyridine-5-monomethylsulfonamide

Method (a): 1 mole of 2-chloropyridine - 5 - monomethylsulfonamide is reacted with 2 moles of trifluoromethylaniline in the presence of copper for 4 hours at 140° C. The reaction product is dissolved in hot acetone, the solution is filtered and the desired sulfonamide precipitates upon addition of an excess of water. The desired product is recrystallized from diluted alcohol. Yield 70%.

Medthod (b): Alternatively, the method of Example 3 is applied, using 2-meta-trifluoromethylanilino-pyridine-5-sulfonic acid as starting material. The desired product precipitates upon addition of water and is recrystallized from diluted ethanol. Yield: 70–80%. m.p. 146–147° C.

Elementary analysis:

Calculated: C 47.13%; H 3.65%; N 12.68%; S 9.68%

Found: C 47.01% H 3.72%; N 12.53%; S 9.90%

EXAMPLE 13

Preparation of 2-meta-trifluoromethylanilino-pyridine-5-dimethylsulfonamide

The method (a): of Example 12 is applied except that 2 - chloropyridine-5-dimethylsulfonamide is used as starting material.

The method (b) of Example 12 is applied by reacting 2-meta-trifluoromethylanilino-pyridine - 5 - sulfonic acid with dimethylamine $NH(CH_3)_2$.

Yield: 70.80% m.p.: 130–131° C.

Elementary analysis:

Calculated: C 48.69%; H 4.09%; N 12.17% S 9.28%

Found: C 48.60%; H 4.15%; N 12.31%; S 9.30%

EXAMPLE 14

Preparation of 2-meta-trifluoromethylanilino-pyridine-5-hydroxyethylsulfonamide

The method (a) of Example 12 is applied except that 2-chloropyridine - 5 - hydroxyethylsulfonamide is used as starting material.

Alternatively, the method (b) is applied by reacting 2-meta-trifluoromethylanilino-pyridine-5-sulfonic acid with a 30% aqueous solution of hydroxyethylamine. The desired product is recrystallized from diluted ethanol. Yield: 70%. m.p. 129° C.

Elementary analysis:

Calculated: C 46.54%; H 3.90%; N 11.63%; S 8.87%

Found: C 46.49%; H 3.97%; N 11.40%; S 9.02%

EXAMPLE 15

Preparation of 2-meta-trifluoromethylanilino-pyridine-5-morpholino sulfone

Method (a): The following mixture is heated for 4 hours at 140° C. and in the presence of copper powder: 0.1 mole of 2 - chloropyridine-5-morpholino sulfone 0.2 mole of meta-trifluoromethylaniline.

The reaction product is dissolved in the warm state in acetone hydrated with 10% water. After filtration, the desired sulfone is precipitated by addition of an excess of water. The precipitate is dissolved in diluted HCl and the solution is heated to boiling in the presence of active carbon. After filtration, the solution is evaporated until a sirupous liquid is obtained. The latter is extracted with water, the desired sulfone precipitates and is recrystallized from diluted methanol. Yield: 60%.

Method (b): The method of Example 5 is applied, using 2 - meta-trifluoromethylanilino-pyridine-5-sulfonic acid as starting material. Yield: 60–70%. m.p. 145° C.

Elementary analysis:

Calculated: C 49.61%; H 4.16%; N 10.85%; S. 8.28%

Found: C 49.50% H 4.19%; N 10.74; S 8.32%

EXAMPLE 16

Preparation of 2-meta-trifluoromethylanilino-pyridine-5-N-methylpiperazino-sulfone

The method of Examples 3 and 6 is applied using 2-meta-trifluoromethylanilino - pyridine-5-sulfonic acid as starting material. However, the desired sulfone already crystallizes by evaporation of the acetone which was added to the sulfochloride residue left after distillation of $OPCl_3$. The desired product is collected, recrystallized from diluted alcohol containing a little amount of ammonia. Yield: 60–70%. m.p. 162° C.

Elementary analysis:

Calculated: C 50.99%; H 4.78; N 13.99%; S 8.01%

Found: C 51.08; H 5.00%; N 13.87%; S 8.10%

EXAMPLE 17

Preparation of 2-meta-trifluoromethylanilino-pyridine-5-(2'-methyl-3'-chlorophenyl) sulfonamide

10 g. of 2 - meta-trifluoromethyanilino-pyridine-5-sulfonic acid are transformed into the corresponding sulfochloride by the usual method using PCl_5 and $OPCl_3$. The sulfochloride is separated from the $OPCl_3$ and extracted with 30 ml. of acetone and then 30 ml. of pyridine. An abundant precipitate sometimes appears and is eliminated by filtration. The filtrate is decomposed dropwise and with constant stirring into a 10% solution of metachlorotoluidine in acetone, 2 mols of amine being used for 1 mole of starting sulfonic acid. The mixture is allowed to react for 0.5 hour with stirring. The solvents are distilled off and the residue is extracted with diluted HCl. The mixture is vigorously stirred and the desired sulfonamide is collected by filtration. The product highly coloured is purified by dissolution in alcohol, heating in the presence of active carbon, filtration and precipitation by addition of water. The sulfonamide is collected, dissolved in a mixture of absolute ethanol and benzene and dehydrated by partial distillation of the solvents. Petroleum ether (b.p.) 100–140° C.) is added and the mixture is further evaporated at ambient temperature. In this way, a well crystallized product is obtained. When necessary, the substance may be further recrystallized from petroleum ether (b.p. 100–140° C.). Yield: 60%. m.p. 159–160° C.

Elementary analysis:

Calculated: C 51.65%; H 3.42; N 9.51%; S 7.26%; Cl 8.02%

Found: C 51.75%; H 3.43%; N 9.40%; S 7.40%; Cl 8.17%

EXAMPLE 18

Preparation of 2-meta-trifluoromethylanilino-pyridine-5-N-acetylsulfonamide

15 g. of 2-meta-trifluoromethylanilino-pyridine-5-sulfonamide are dissolved in 75 g. of pyridine and 75 g. of acetic anhydride. The solution is stirred from time to time in a closed container for 2 hours. 1 liter of water is added thereto, a precipitate is formed, collected, washed with water and suspended in 2 liters of 5% $NaHCO_3$ solution. After a vigorous stirring, the mixture is filtered to eliminate the unreacted sulfonamide and the filtrate is neutralized by HCl. The desired sulfonamide precipitates and may be recrystallized from diluted alcohol. Yield: 60–70%. m.p. 232° C.

Elementary analysis:

Calculated: C 46.79%; H 3.37%; N 11.69%; S 8.92%

Found: C 46.56%; H 3.49%; N 11.59%; S 8.88%.

EXAMPLE 19

Preparation of 4-meta-trifluoromethylanilino-pyridine-5-sulfonic acid

4-chloropyridine-5-sulfonic acid is first prepared by reacting for 4 hours at 140° C. the following mixture: 10 g. of 4 - hydroxypyridine-5-sulfonic acid, 18 g. of PCl_5 and a little amount of $OPCl_3$, the sulfochloride thus formed being hydrated by means of boiling water to form the desired 4-chloropyridine-5-sulfonic acid.

The latter product in an amount of 0.1 mole is reacted with 0.2 mole of meta-trifluoromethylaniline in the presence of 500 mg. of copper powder for 4 hours at 140–150° C. The reaction mixture is triturated together with acetone, heated to boiling and water is added to it until almost complete dissolution. The thus obtained mixture is filtered and evaporated under reduced pressure. The desired sulfonic acid crystallizes. The product is then treated with active carbon in diluted alcohol, and after filtration it is recrystallized from the same solvent. Yield: 70–80%. m.p. 267° C.

Elementary analysis:

Calculated: C 45.28%; H 2.85%; N 8.80%; S 10.07%

Found: C 45.40%; H 2.71%; N 8.93%; S 10.24%

EXAMPLE 20

Preparation of 4-meta-trifluoromethylanilino-pyridine-5-sulfonamide

The following mixture is heated for 0.5 hour at 130° C.: 10 g. of 4-meta-trifluoromethylanilino pyridine-5-sulfonic acid, 10 g. of PCl_5 and a little amount of $OPCl_3$. The $OPCl_3$ is distilled off. The residue is extracted with 30 ml. of acetone, decomposed in the cold state in 200 ml. of concentrated ammonia. After 0.5 hour, the acetone is distilled off and the excess of NH_3 which causes precipitation of the desired sulfonamide. If the product is coloured, it is purified by heating in HCl mixture in the presence of carbon. After filtration, the desired sulfonamide is precipitated by addition of ammonia. Diluted ethanol is used as a solvent for recrystallisation. Yield: 60–70%. m.p. 200° C.

Elementary analysis:

Calculated: C 45.43%; H 3.18%; N 10.11%; S 13.24%

Found: C 45.70%; H 3.27%; N 10.15%; S 13.12%

EXAMPLE 21

Preparation of 4-meta-trifluoromethylanilino-pyridine-5-monomethylsulfonamide

The sulfochloride of 4-meta-trifluoromethylanilino-pyridine-5-sulfonic acid is prepared as in Example 20. An acetonic solution is obtained, decomposed in a large amount of 30% aqueous solution of NH_2CH_3. After 0.5 hour at rest, followed by a partial evaporation the desired sulfonamide precipitates. It is then recrystallized from diluted ethanol. Yield: 60–70%. m.p. 183° C.

Elementary analysis:

Calculated: C 47.13%; H 3.65%; N 12.68% S 9.68%

Found: C 47.15%; H 3.49%; N 12.82%; S 9.48%

EXAMPLE 22

Preparation of 4-meta-trifluoromethylanilino-pyridine-5-morpholino sulfone

The sulfochloride of 4-meta-trifluoromethylanilino-pyridine-5-sulfonic acid is prepared as in Example 20. The remaining steps are as in Example 5. Diluted ethanol is used as a solvent for recrystallization. Yield: 60–70%; m.p. 128° C.

Elementary analysis:

Calculated: C 49.61%; H 4.16%; N 10.85%; S 8.28%

Found: C 49.39%; H 4.11%; N 10.93%; S 8.38%

EXAMPLE 23

Preparation of 4-meta-trifluoromethylanilino-pyridine-5-methylpiperazinyl-sulfone

The sulfochloride of 4-meta-trifluoromethylanilino-pyridine-5-sulfonic acid is first prepared as in Example 20. Thereafter, the method of Example 16 is applied. Sometimes the desired product is separated as an oily precipitate which crystallizes with difficulty. It is then convenient to dissolve the product in alcohol and to add, in the warm state, water until persistant clouding. Alternately, the method of Example 6 may be followed. Yield: 60%; m.p. 112° C.

Elementary analysis:

Calculated: C 50.99%; H 4.78%; N 13.99%; S 8.01%

Found: C 50.80%; H 4.91%; N 13.69%; S 8.12%

EXAMPLE 24

Preparation of 4-meta-trifluoromethylanilino-pyridine-5-metachlorophenylsulfonamide

The sulfochloride of 4-meta-trifluoromethylanilino-pyridine-5-sulfonic acid is prepared as in Example 20. It is treated with 30 ml. of acetone and 30 ml. of pyridine. The method of Example 17 is then applied except that a solution of metachloraniline is used instead of metachlorotoluidine. Yield about 60%. m.p. 138° C.

Elementary analysis:

Calculated: C 50.33%; H 3.06%; N 9.82%; S 7.49%; Cl 8.29%

Found: C 50.60%; H 3.27%; N 10.00%; S 7.38%; Cl 8.24%

EXAMPLE 25

Preparation of 4-meta-trifluoromethylanilino-pyridine-5-N-acetylsulfonamide

The method of Example 8 is applied, using 4-meta-trifluoromethylanilino pyridine-5-sulfonamide as the starting material. The desired product is obtained with a similar yield as in said example. It may be crystallized from water. To obtain an anhydrous product, the sulfonamide is dried in a drying oven in vacuo at 110° C. m.p. 176–178° C.

Elementary analysis:

Calculated: C 46.79%; H 3.37%; N 11.69%; S 8.92%

Found: C 46.49%; H 3.42%; N 11.70%; S 8.18%

EXAMPLE 26

Preparation of 4-carboxypyridine-5-sulfonimide

Method a: 13 g. of 4-picoline-5-sulfonamide are dissolved in 500 ml. of water and 28 g. of $KMnO_4$ are added thereto. The solution is stirred and heated to 60–70° C. until the permanganate is decolourized. The mixture is filtered in the hot state to remove the manganese dioxide, neutralized with HCl and evaporated under reduced pressure to give by dehydration the desired carboxysulfonimide which precipitates. Yield: 30–40%. m.p. 345–347° C.

Method b: 10 g. of 4-carboxypyridine-5-sulfonic acid are treated with 10 ml. of dimethylformamide and 100 ml. of thionyl chloride under boiling and reflux heating conditions. After 3 hours, a clear solution is obtained. The solution is evaporated to dryness under reduced pressure. The residue is treated with an inert solvent and with NH_3. The solvent is evaporated, the desired carboxysulfonimide is collected, recrystallized from water in the presence of active carbon.

Elementary analysis:

Calculated: C 39.13%; H 2.19%; N 15.21%; S 17.41%

Found: C 39.20%; H 2.40%; N 15.48%; S 17.23%

EXAMPLE 27

Preparation of 2-(4'-methyl-1'-piperazinyl)-pyridine-3-sulfonamide

The following mixture is placed into a 100 ml. flask 10 g. of 2-chloro-pyridine-3-sulfonamide, from 30 to 40 ml. of toluene and 10 ml. of 1-methyl piperazine. Said mixture is heated to boiling and refluxed for 4 hours. The reaction mixture is extracted with water, rendered alkaline with NaOH and purified with active carbon. After filtration, the solution is brought to pH 7–8 by addition of HCl. The desired sulfonamide crystallizes, is filtered and dried. Yield: 60%. m.p. 129–130° C.

Elementary analysis:

Calculated: C 46.87%; H 6.25%; N 21.87%; S 12.50%

Found: C 46.75%; H 6.25%; N 21.71%; S 12.44%

EXAMPLE 28

Preparation of 2-(4'-methyl-1'-piperazinyl)-pyridine-3-methylsulfonamide

2-chloropyridine-3-methylsulfonamide is first prepared as in Example 2, method b, except that a 40% aqueous solution of methylamine is used instead of the solution of NH_3. Yield 60–70%. m.p. 83.5–84.5° C.

Elementary analysis:

Calculated: C 34.87%; H 3.39%; N 13.56%; S 15.5%; Cl 17.19%

Found: C 34.61%; H 3.47%; N 13.42%; S 15.61%; Cl 17.12%

The desired piperazinylsulfonamide is now prepared as follows: The following mixture is placed into a 100 ml. flask: 10 g. of 2-chloro-pyridine-3-methylsulfonamide, 30 to 40 ml. of toluene and 10 ml. of 1-methylpiperazine. Said mixture is refluxed for 4 hours. The reaction mixture is evaporated under reduced pressure. The residue is taken up with water, rendered strongly alkaline with NaOH and extracted with $CHCl_3$. The extracts are dehydrated, evaporated under reduced pressure to give an oily residue which is extracted with petroleum benzine (b.p. 50–75° C.). The precipitate obtained is filtered off, washed and recrystallized from petroleum benzine (b.p. 50–75° C.). Yield: 60–70%. m.p. 83.5–85° C.

Elementary analysis:

Calculated: C 48.89%; H 6.67%; N 20.74%; S 11.85%

Found: C 48.67%; H 6.65%; N 20.56%; S 11.91%

EXAMPLE 29

Preparation of 2-(4'-methyl-1'-piperazinyl)-pyridine-3-dimethylsulfonamide

2-chloropyridine-3-dimethylsulfonamide is first prepared as in Example 2, method b, except that a 25–30% aqueous solution of dimethylamine is used instead of the solution of NH_3. Yield: 60–70%. m.p. 39.5–40.5° C.;

Elementary analysis:

Calculated: C 38.09%; H 4.08%; N 12.70%; S 14.51%; Cl 16.10%

Found: C 37.94%; H 4.19%; N 12.61%; S 14.37%; Cl 16.06%

The desired piperazinylsulfonamide is now prepared by the method of Example 28 using 2-chloro-pyridine-3-dimethylsulfonamide as starting material. Yield: 60–70%. m.p. 78–79° C.

Elementary analysis:

Calculated: C 50.70%; H 7.04%; N 19.71%; S 11.26%

Found: C 50.49%; H 7.26%; N 19.56%; S 11.08%

EXAMPLE 30

Preparation of 2-(4'-methyl-1'-piperazinyl)-pyridine-3-ethylsulfonamide

2-chloro-pyridine-3-ethylsulfonamide is first prepared as in Example 2, method b, except that a 30% alcoholic solution of ethylamine is used instead of the NH_3 solution Yield: 70–80%. m.p. 83.5–85° C.

Elementary analysis:

Calculated: C 38.09%; H 4.08%; N 12.70%; S 14.51%; Cl 16.10%

Found: C 37.87%; H 4.12%; N 12.65%; S 14.66%; Cl 16.03%

The desired piperazinylsulfonamide is then prepared by the method of Example 28 using 2-chloro-pyridine-3-ethylsulfonamide as starting material. Yield: 70%. m.p. 93–94.5° C.

Elementary analysis:

Calculated: C 50.70%; H 7.04%; N 19.71%; S 11.26%

Found: C 50.74%; H 7.14%; N 19.57%; S 11.17%

EXAMPLE 31

Preparation of 2-(4'-methyl-1'-piperazinyl)-pyridine-3-diethylsulfonamide dihydrochloride.

2-chloro-pyridine-3-diethylsulfonamide is first prepared as in Example 2, method b, using diethylamine (30% aqueous solution) instead of ammonia. After 0.5 hours, the aqueous solution consisting of the reaction mixture is evaporated, neutralized with $NaHCO_3$ if necessary and extracted with CH_2Cl_2. The latter is evaporated under reduced pressure. The oily residue is distilled and the desired product passes at 143–145° C. under 0.1 mm. of Hg and crystallyzes in the receptor container. Yield: 60%. m.p. 46–47° C.

Elementary analysis:

Calculated: C 43.46%; H 5.23%; N 11.27%; S 12.87%; Cl 14.29%

Found: C 43.24%; H 5.39%; N 11.16%; S 12.71%; Cl 14.21%

The desired piperazinylsulfonamide is then prepared by the method of Example 28 using 2-chloro-pyridine-3-diethylsulfonamide as starting material. The product instead of being precipitated with petroleum ether (b.p. 50–75° C.) is extracted with acetone and precipitated as a dihydrochloride by passage of gaseous HCl through the acetone solution. Yield: 60% m.p. 161–163° C.

Elementary analysis:

Calculated: C 43.64%; H 6.75%; N 14.54%; S 8.31%; Cl 20.11%

Found: C 43.51%; H 6.91%; N 14.45%; S 8.10%; Cl 19.88%

EXAMPLE 32

Preparation of 2-(4'-methyl-1'-piperazinyl)-pyridine-3-isopropylsulfonamide

2-chloro-pyridine-3-isopropylsulfonamide is first prepared as in Example 2, method b, using a 30% aqueous solution of isopropylamine instead of aqueous ammonia. Yield: 60–70%. m.p. 116–118° C.

Calculated: C 40.94%; H 4.68%; N 11.99%; S 13.70%; Cl 15.20%

Found: C 40.87%; H 4.96%; N 11.84%; S 13.61%; Cl 15.12%

The desired piperazinylsulfonamide is prepared by the method of Example 28 using 2-chloro-pyridine-3-isopropylsulfonamide as the starting material. Yield: 60–70%. m.p. 109–110° C.

Elementary analysis:

Calculated: C 52.35%; H 7.38%; N 18.79%; S 10.74%

Found: C 52.54%; H 7.56%; N 18.62; S 10.88%

EXAMPLE 33

Preparation of 2-(4'-methyl-1'-piperazinyl)-pyridine-3-(4'-methyl-1'-piperazinyl)-sulfonamide dihydrochloride

The method of Example 2, method b, is applied for reacting 2-chloropyridine-3-sulfonic acid with PCl_5 and $OPCl_3$. However, the 2-chloropyridine-3-sulfochloride thus obtained in an acetonic solution, instead of being poured into an ammonia solution, is poured into a toluenic solution of 1-methylpiperazine. After reaction in the cold state, the mixture is refluxed for 4 hours. The desired sulfonamide is isolated in the form of the dihydrochloride thereof by applying the method described in Example 31. Yield: about 50%. m.p. 275–277° C.

Elementary analysis:

Calculated: C 43.68%; H 6.55%; N 16.99%; S 7.77%; Cl 17.23%

Found: C 43.51%; H 6.78%; N 16.72%; S 7.58%; Cl 17.16%

EXAMPLE 34

Preparation of 2-(4'-methyl-1'-piperazinyl)-pyridine-5-sulfonamide

The following mixture is placed into a 100 ml. flask: 10 g. of 2-chloro-pyridine-5-sulfonamide and 15 g. of 1-methylpiperazine hydrochloride. The temperature is raised slowly up to 80° C. At the moment said temperature is reached, the reaction mass is melted and enters into reaction with spontaneous raise of the temperature. The reaction mixture is then heated to 150° C. and maintained at said temperature for 15 minutes. After cooling, the reaction mass is dissolved in water rendered alkaline with soda. The pH is then adjusted to 8. The desired sulfonamide precipitates. The precipitate is collected, washed with cold water and dried. Yield: 60%. m.p. 199.5–201° C.

Elementary analysis:

Calculated: C, 46.87%; H, 6.25%; N, 21.87%; S 12.50%

Found: C 46.65%; H 6.47%; N 21.74%; S 12.63%

EXAMPLE 35

Preparation of 2-(4'-methyl-1'-piperazinyl)-pyridine-5-methylsulfonamide

The method of Example 34 is applied using this time 2-chloro-pyridine-5-methylsulfonamide as starting material. The desired product is however isolated as follows: The aqueous alkaline solution is extracted with $CHCl_3$. The $CHCl_3$ solution is evaporated under reduced pressure and the desired product is precipitated by means of petroleum ether (b.p. 50–75° C.). Yield: 60%.

Elementary analysis:

Calculated: C 48.89%; H 6.67%; N 20.74%; S 11.85%

Found: C 48.71%; H 6.83%; N 20.61%; S 11.73%

EXAMPLE 36

Preparation of 2-(4'-methyl-1'-piperazinyl) pyridine-5-dimethylsulfonamide

The method of Example 35 is applied, using this time 2-chloro-pyridine-5-dimethylsulfonamide as starting material. The isolation method is also as in Example 35. Yield: 60%.

Elementary analysis:

Calculated: C 50.70%; H 7.04%; N 19.71%; S 11.26%

Found: C 50.61%; H 7.18%; N 19.26%; S 11.13%

EXAMPLE 37

Preparation of 2-(4'-methyl-1'-piperazinyl)-pyridine-5-ethylsulfonamide

The method of Example 28 is applied using however 2-chloro-pyridine-5-ethylsulfonamide as starting material. Yield: 60–70%. m.p. 133.5–135° C.

Elementary analysis:

Calculated: C 50.70%; H 7.04%; N 19.71%; S 11.26%

Found: C 50.52%; H 7.30%; N 19.83%, S 11.32%

EXAMPLE 38

Preparation of 2-(4'-methyl-1'-piperazinyl)-pyridine-5-diethylsulfonamide

The method of Example 28 is applied using however 2-chloro-pyridine-5-diethylsulfonamide. Yield: 60–70%. m.p. 105–106° C.

Elementary analysis:
Calculated: C 53.84%; H 7.69%; N 17.95%; S 10.26%
Found: C 53.66%; H 7.84%; N 17.82%; S 10.11%

EXAMPLE 39

Preparation of 2-(4'-methyl-1'-piperazinyl)-pyridine-5-isopropylsulfonamide

The method of Example 28 is applied except that 2-chloro-pyridine-5-isopropylsulfonamide is used as starting material. Yield: 60–70%. m.p. 132–133.5° C.

Elementary analysis:
Calculated: C 52.35%; H 7.38%; N 18.79%; S 10.74%
Found: C 52.15%; H 7.51%; N 18.61% S 10.89%

EXAMPLE 40

Preparation of 2-(4'-methyl-1'-piperazinyl)-3-cyano-pyridine hydrochloride

The method of Example 31 is applied except that 2-chloro-3-cyano-pyridine is used as starting material. Before precipitating the hydrochloride, the solution of extraction is evaporated under reduced pressure to remove the excess of 1-methylpiperazine. The residue is then extracted with acetone and the method is further applied as in Example 31. Yield: 60%. m.p. 221–222.5° C.

Elementary analysis:
Calculated: C 55.46%; H 6.30%; N 23.48%
Found: C 55.30%; H 6.53%; N 23.31%

EXAMPLE 41

Preparation of 2-(4'-methyl-1'-piperazinyl)-nicotinic acid

A solution of 10% NaOH is added to 10 g. of 2-(4'-methyl-1'-piperazinyl)-3-cyano-pyridinehydrochloride and refluxed for 6 hours. The mixture is allowed to cool and brought to pH 8 by means of concentrated HCl. After evaporation to dryness under reduced pressure, the residue is extracted with a mixture of equal parts of absolute alcohol and benzene. The liquid of extraction is then evaporated under reduced pressure until the desired nicotinic acid crystallizes as white crystals. Yield: 60%; m.p. 269° C.

Elementary analysis:
Calculated: C 59.73%; H 6.78%; N 19.00%
Found: C 59.61%; H 6.97%; N 18.84%

EXAMPLE 42

Preparation of 2-(4'-methyl-1'-piperazinyl)pyridine-3-diethylcarboxamide and the hydrochloride thereof

2-chloro-pyridine-3-diethyl-carboxamide is first prepared by either of the following methods:

Method 1.—The following mixture is placed into a 100 ml. flask provided with two necks: 10 g. of diethyl-nicotinamide-1-oxide and 50 ml. of $OPCl_3$. The mixture is heated to 120° C. and 30 g. of PCl_5 are added little by little. The temperature is maintained at 120° C. for 1.5 hour. After cooling, the $OPCl_3$ is evaporated under reduced pressure. The oily residue is poured onto ice and neutralized with $NaHCO_3$. It is extracted with $CHCl_3$. The chloroformic solution is evaporated under reduced pressure and the residue is distilled off in vacuo. The desired 2-chloro-diethylcarboxamide passes at 150–155° C. under 0.4–0.5 mm. of Hg. Yield: 60%.

Method 2.—The following mixture is refluxed for 3 hours: 10 g. of 2-chloro-nicotinic acid and 80 ml. of thionyl chloride. The reaction mixture is evaporated to dryness, extracted with 100 ml. of hexane, again evaporated to dryness and the same operation is repeated two further times. The residue is extracted with 50 ml. of acetone and the solution thus obtained is poured dropwise and with stirring into a mixture of 20 ml. of diethylamine and 80 ml. of benzene. After addition, the reaction mixture is evaporated under reduced pressure. The residue is extracted with water and sodium hydroxide and then with $CHCl_3$. The chloroformic solution is dried on dry Na_2SO_4 and evaporated under reduced pressure. The residue is distilled in vacuo. The desired 2-chloro-diethylcarboxamide passes at 150–155° C. under 0.4–0.5 mm. of Hg.

Elementary analysis:
Calculated: C 56.47%; H 6.12%; N 13.18%; Cl 16.70%
Found: C 56.34%; H 6.23%; N 13.29%; Cl 16.69%

The desired 2-(4'-methyl-1'-piperazinyl)-pyridine-3-diethylcarboxamide is then prepared as follows:

10 g. of 2-chloro-pyridine-3-diethylcarboxamide, 30–40 ml. of toluene and 10 g. of 1-methyl-piperazine are placed in a 100 ml. flask. The reaction mixture is refluxed for 4 hours. A solution is thus obtained and is evaporated under reduced pressure. The residue is taken with H_2O and NaOH and is then extracted with $CHCl_3$. The chloroformic extracts are evaporated under reduced pressure and the residue thereof is distilled in vacuo. The product passes at about 175° C. under 0.4–0.5 mm. of Hg. It is taken or extracted with anhydrous acetone and dry gaseous HCl is bubbled through the acetonic solution. The desired product precipitates as its hydrochloride: Yield: 70% m.p. 225–226.5° C.

Elementary analysis:
Calculated: C 57.58%; H 8.00%; N 17.98%
Found: C 57.79%; H 8.09%; N 17.82%

EXAMPLE 43

Preparation of 2-(4'-methyl-1'-piperazinyl)-pyridine-5-sulfonic acid

10 g. of 2-chloro-pyridine-5-sulfonic acid, 15 ml. of 1-methyl-piperazine and 0.5 g. of copper powder are placed into a 100 ml. flask. The mixture is heated at 140–150° C. for 5 hours. It is then taken with methanol, the copper is filtered off, the solution is evaporated to dryness and the residue is taken with absolute ethanol to recrystallize the desired product. Yield: 70%. M.P. 322–324° C.

Elementary analysis:
Calculated: C 46.69%; H 5.83%; N 16.34%; S 12.45%
Found: C 46.51%; H 6.01%; N 16.21%; S 12.39%

EXAMPLE 44

Preparation of 2-(4'-methyl-1'-piperazinyl)-pyridine-5-diethylcarboxamide and the hydrochloride thereof

The method of Example 42 is applied, using 2-chloro-pyridine-5-diethylcarboxamide as starting material and refluxing the reaction mixture for 8 hours.

Upon distillation, the desired product passes at 220–230° C. under 1.5 mm. of Hg.

The hydrochloride thereof is precipitated in the same way as in Example 42.

EXAMPLE 45

Dragées

Core	Mg.
4-meta - trifluoromethylanilino - pyridine-5-sulfonamide	50.0
Colloidal silica	5.0
Lactose	42.5
Polyvidone	3.5
Glycerol	0.5
Maize starch	8.0
Talc	10.0
Magnesium stearate	0.5

Coating	Mg.
Gum lac	2.0
Gum arabic	5.4
New-Coccine	0.1
Talc	13.0
Colloidal silica	9.5
Saccharose	50.0

for one dragee

EXAMPLE 46

Tablets

Core	Mg.
2 - meta-trifluoromethylanilino-pyridine - 3-sulfonamide	200.0
Colloidal silica	17.0
Stearic acid	4.0
Gelatine	4.0
Glycerol	1.6
Maize starch	52.0
Magnesium stearate	1.4

for one tablet

EXAMPLE 47

Capsules

	Mg.
2-(4'-methyl - 1' - piperazinyl)-pyridine-3-dimethyl-sulfonamide	100.0
Lactose	120.0
Rice starch	30.0
Maize starch	30.0
Magnesium stearate	5.0
Envelope	
Gelatine	78.0
Tartrazine	0.2

for one capsule.

EXAMPLE 48

Suppositories

	Mg.
4 - metatrifluoromethylanilinopyridine - 5 - sulfonic acid	300
Witepsol H 12 mass [1] for one suppository	600

[1] A mixture of triglycerides and partial glycerides of saturated fatty acids (C_{12}–C_{18}) originating from plants, furnished by Dynamit Nobel AG, Köln-Mülheim, Western Germany.

EXAMPLE 49

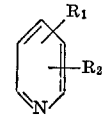
Vials

	Mg.
2-meta-trifluoromethylanilinopyridine - 5 - sulfonic acid	20.0
Natrium chloride	85.0
acid	20.0

Distilled water to form 10.0 ml.
for one vial.

What we claim is:

1. A pyridine compound of the formula:



wherein R_1 in the 3-position represents a sulfonamido group of the formula SO_2NH—Ac, wherein Ac represents an alkanoyl group having from 2 to 4 carbon atoms, when R_2 in the 4- or 6-position represents an anilino group, which may be substituted with one or more members selected from the group consisting of a lower alkyl group, a trifluoromethyl group, a halogen atom, and a nitro group.

2. A compound according to claim 1:
2-meta-trifluoromethylanilino-pyridine - 3 - N - acetyl sufonamide.

3. A compound according to claim 1:
2-meta-trifluoromethylanilino-pyridine - 5 - N - acetyl sulfonamide.

4. A compound according to claim 1:
4-meta-trifluoromethylanilino - pyridine - 5 - N - acetyl-sulfonamide.

References Cited

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ALAN L. ROTMAN, Primary Examiner

U.S. Cl. X.R.

260—247.1, 243 R, 243 A, 268 H, 294.8 C, 204.9, 295.5-A, 301; 424—248, 250, 263

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 3,819,639 Dated June 25, 1974

Inventor(s) Jacques E. Delarge; Leopold N. J. V. Thunus; Charles L. Lapiere and Andre H. E. Georges

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 22, line 18, change "3-position" to read -- 3- or 5-position--

Column 22, line 21, change "4- or 6-position" to read -- 2- or 4-position--

Signed and sealed this 8th day of April 1975.

(SEAL)
Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents
and Trademarks

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