United States Patent

[11] 3,609,187

[72] Inventors George G. I. Moore
White Bear Lake;
Alvin C. Conway, North St. Paul, both of Minn.

[21] Appl. No. 816,090
[22] Filed Apr. 14, 1969
[45] Patented Sept. 28, 1971

[73] Assignee Minnesota Mining and Manufacturing Company
St. Paul, Minn.

[54] N,N-DISUBSTITUTED TRIFLUOROMETHANESULFONAMIDES
8 Claims, No Drawings

[52] U.S. Cl. ..... 260/556 F, 260/465 D, 260/479 R, 260/543 R, 260/559 R, 260/558 D, 260/558 R, 424/321
[51] Int. Cl. C07c 143/74
[50] Field of Search ..... 260/56, F, 556 C, 465 D, 479, 556 AC, 479 R

[56] References Cited

UNITED STATES PATENTS

2,075,359	3/1937	Salzberg et al.	424/250
2,995,542	8/1961	Brown	260/556 F

Primary Examiner—Henry R. Jiles
Assistant Examiner—S. D. Winters
Attorney—Kinney, Alexander, Sell, Steldt & Delahunt

ABSTRACT: By reacting N-alkyl- and N-alkenyl-trifluoromethanesulfonamides with certain aroyl halides or anhydrides there are obtained N-aroyl-N-alkyl- and N-aroyl-N-alkenyltrifluoromethanesulfonamides having physiological activity as anticonvulsant agents.

N,N-DISUBSTITUTED TRIFLUOROMETHANESULFONAMIDES

BACKGROUND OF THE INVENTION

1. Field of the Invention

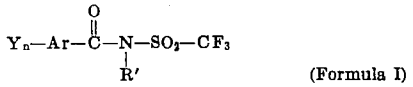
This invention relates to substituted sulfonamides, and more particularly to N,N-disubstituted trifluoromethanesulfonamides wherein one of the nitrogen substituents is an aroyl radical, and to compounds useful as anticonvulsant agents.

2. Description of the Prior Art

Certain N,N-disubstituted perfluoroalkanesulfonamides are known to the art, such as those described in U.S. Pat. Nos. 2,803,615; 2,803,656; 2,809,990; 2,841,573; 3,147,064; 3,147,066 and 2,995,542. None of these patents describe trifluoromethanesulfonamides substituted by an aroyl group on the nitrogen of the sulfonamido group. All of these patents require at least four carbon atoms in the perfluoroalkyl group. No suggestion of physiological activity of the compounds of the prior art patents is disclosed.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to compounds of the formula:



(Formula I)

wherein R′ is lower alkyl or lower alkenyl, Ar is phenyl or naphthyl, Y is lower alkyl, lower haloalkyl, lower alkoxy, phenyl, halogen, nitro, cyano or acetoxy and *n* is zero to three.

Compounds wherein R′ is methyl are presently preferred.

The term "lower" when applied to the alkyl, haloalkyl and alkoxy radicals of this invention refers to radicals containing from one to about four carbon atoms. Presently preferred as substituents on the aryl group are those lower alkyl, haloalkyl, alkoxy and alkylsulfonyl radicals containing one carbon atom, because starting materials to make compounds containing these substituents are generally more readily available.

The following are exemplary of compounds of the invention:

N-(3-fluorobenzoyl)-N-(n-propyl)trifluoromethanesulfonamide

N-benzoyl-N-allyltrifluoromethanesulfonamide

N-(2-naphthoyl)-N-methyltrifluoromethanesulfonamide

N-(4-methylsulfonylbenzoyl)-N-(n-butyl)trifluoromethanesulfonamide

N-(3-trifluoromethylbenzoyl)-N-isopropyltrifluoromethanesulfonamide

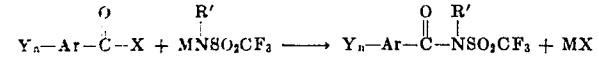
N-(p-biphenylcarbonyl)-N-methyltrifluoromethanesulfonamide

N-(4-nitrobenzoyl-N-cyclopropyltrifluoromethanesulfonamide

N-(4-cyanobenzoyl)-N-methyltrifluoromethanesulfonamide

These compounds are made by the methods specifically described hereinafter, from known starting materials.

The compounds of the invention are prepared conveniently by the reaction of an aroyl halide with an N-alkyl- or N-alkenyl-trifluoromethanesulfonamide or its salt as shown in the following equation:



(Equation I)

In this equation, Ar, R′, Y and *n* are as defined above, X is halogen, preferably chlorine, since the aroyl chlorides are generally more conveniently available and M is preferably hydrogen or a metal, preferably an alkali metal.

It is preferred that the reaction be run in the presence of base, although base is not necessary, and preferably in a non-reactive solvent. Generally, this solvent has been benzene or dichloromethane, but other solvents including alkyl ketones, esters, mono- and diglyme, alkanes, other chlorinated solvents and the like can be used. It is preferred that these solvents dissolve most of the reactants to facilitate homogeneous reaction.

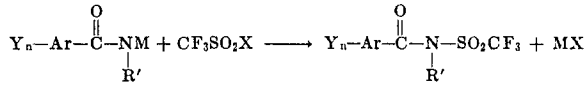
Bases which are suitable include salts of weak acids such as sodium acetate and sodium carbonate and organic tertiary amines such as triethylamine is preferred. The reaction is preferably run under anhydrous conditions, and when very reactive acyl halides are used, under an atmosphere of a relatively inert gas such as nitrogen. Other equivalent anhydrous conditions will be apparent to those skilled in the art.

The reaction between the aroyl halide and the N-alkyl- or N-alkenyltrifluoromethanesulfonamide is generally quite rapid at room temperature, although stirring is continued for up to several hours in order to insure completion of the reaction. Refluxing and/or extended reaction periods may be useful to obtain reaction of relatively unreactive pairs of reactants.

The aroyl halides (and/or corresponding acids, from which the halides are prepared) are known to the art. The method for the preparation of the N-alkyl- and N-alkenyltrifluoromethanesulfonamide is known to the art.

These reactions may also be run in high pressure reactors, without solvent.

An alternative route to some of the compounds of this invention is available. This consists of the reaction of an appropriate amide, or its salt, with a trifluoromethanesulfonyl halide, as shown in the following equation.



In this equation, M, R′, Ar, Y, *n* and X are as defined above. However, this route is generally not preferred. Other routes, such as the reaction of ketenes with N-alkyl- or N-alkenyltrifluoromethanesulfonamide, and the reaction of anhydrides with N-alkyl- or N-alkenyltrifluoromethanesulfonamides, are also possible routes to the compounds of the invention.

For general use as anticonvulsants, the compounds of the present invention are preferably administered orally.

The amounts of the compounds of Formula I which are to be administered will depend on several factors including the weight of the warm-blooded animal recipient and the route of administration employed. Generally, the compounds of the invention are effective in doses of 0.1 to 20 milligrams per kilogram daily. The amounts can be given in single or multiple doses, as required. The particular dosage for any given situation will be apparent to one skilled in the art.

The compounds of Formula I, which are, practically speaking, substantially insoluble in water, are soluble in lower alcohols, glycerin, and the like, and can be suitably formulated in physiologically acceptable solutions and carriers to make tablets, syrups, isotonic solutions, injectable solutions, suppositories and other dosage forms.

In order to examine the efficacy of the compounds of the present invention in the prevention or reduction in severity of convulsive seizures, they were tested by two methods, electroshock and chemically induced shock. More specifically, antagonism of corneal supramaximal electroshock and 1,5-pentamethylenetetrazole-induced seizures was used as the test methods.

The supramaximal electroshock technique is described in detail by Toman, et. al., Journal of Neurophysiology 9:231,(1946).

The production of 1,5-pentamethylenetetrazole-induced seizures is described in detail by Everett and Richards, Journal of Pharmacology and Experimental Therapeutics 81, 402 (1944).

In order to obtain a correlation of the effectiveness of the protection with the lethal hazard, the dose (ED_{50}) that protects 50 percent of the animals at the time of peak antishock

effect is calculated, and is compared to the median lethal dose, LD_{50}. A therapeutic index ($T.I.=LD_{50}/ED_{50}$) is calculated. Several of the most active compounds of the invention have been found to have a therapeutic index greater than 5.

The activity of these compounds is theorized to be the result of inhibition of the enzyme carbonic anhydrase. The theory is supported by positive results in a standard in vitro assay. Thus some of the compounds of the invention can be expected to be useful in a similar fashion to known carbonic anhydrase inhibitors, for example, as diuretics, antiglaucoma agents and in the facilitation of acclimatization to higher altitudes. Certain plant growth modifiers are known to be effective inhibitors of plant carbonic anhydrase.

Some of the compounds of the invention also show activity as diuretics, plant growth modifiers, antimicrobials, insecticides and fungicides. Plant growth modifying activity was determined using screening tests against experimental plantings. Other physiological activities were determined using standard screening methods.

The compounds of the invention are especially advantageous because the duration of their effect is quite long, generally exceeding 48 hours. This permits longer intervals between doses, with no reduction in effectiveness. Alternatively, the repeated administration of lower, acutely subeffective dosages has been demonstrated to result in ultimate complete effectiveness. Thus, subeffective dosages have a cumulative effect.

The effectiveness of many of the compounds of the invention has been examined by the test methods described hereinabove, and all are active anticonvulsant agents, although it will be appreciated that some are more effective than others, The presently preferred compounds of the invention include:

N-(3-bromobenzoyl)-N-methyltrifluoromethanesulfonamide

N-(4-chlorobenzoyl)-N-methyltrifluoromethanesulfonamide and

N-(3-chlorobenzoyl)-N-methyltrifluoromethanesulfonamide

In order to further illustrate the invention the following nonlimiting examples are provided. Melting points are uncorrected.

The N-alkyl- or N-alkenyltrifluoromethanesulfonamides used as intermediates are prepared by methods known to the art. The preparation of such intermediates is illustrated in the following example.

EXAMPLE 1

Dichloromethane (300 ml.) and n-propylamine (76 g., 0.5 mole) in a one-liter flask are cooled using an ice-salt bath and stirred vigorously, and trifluoromethanesulfonyl fluoride (80 g., slight excess) is charged slowly above the solution. After the completion of the addition the reaction is stirred for one hour, then allowed to warm to room temperature. The reaction mixture is washed with 10 percent hydrochloric acid (150 ml.). The dichloromethane layer is dried over magnesium sulfate, filtered and the solvent evaporated in vacuo. The N-(n-propyl)trifluoromethanesulfonamide is distilled, b.p. 98°–100b*L* C./20 mm.

Analysis:	% C	% H
Calculated for $C_4H_8F_3NO_2S$:	25.2	4.2
Found:	25.2	4.3

The following compounds are prepared according to the procedure of example 1.

N-(n-butyl)trifluoromethanesulfonamide, b.p. 94° C./9 mm.

N-methyltrifluoromethanesulfonamide, b.p. 84°–85° C./20 mm.

N-ethyltrifluoromethanesulfonamide, b.p. 78° C./15 mm.

N-cyclopropyltrifluoromethanesulfonamide, b.p. 111° C./35 mm.

N-isopropyltrifluoromethanesulfonamide, b.p. 94°–98° C./20 mm.

N-allyltrifluoromethanesulfonamide, b.p. 50° C./0.2 mm.

EXAMPLE 2

N-Aroyl-N-alkyl or alkenyltrifluoromethanesulfonamides made by the general procedure of equation I:

A mixture of aroyl halide (0.1 mole) and N-alkyl- or alkenyltrifluoromethanesulfonamide (0.1 mole) in a solvent (about 300 ml.) usually benzene or dichloromethane is stirred and triethylamine (0.12 mole) is added. Stirring while cooling or refluxing or at room temperature for one or more hours is followed by successively washing with 300 ml. each of water, 5 percent sodium hydroxide, 5 percent hydrochloric acid and water. The organic layer is dried over magnesium sulfate, then the solvent is removed in vacuo. The product is distilled under vacuum if a liquid or recrystallized if a solid, usually from mixtures of aromatic and aliphatic hydrocarbons such as benzene-hexane.

EXAMPLE 3

Dichloromethane (300 ml.), N-methyltrifluoromethanesulfonamide (16.4 g., 0.10 mole) and 3-chlorobenzoyl chloride (17.5 g., 0.10 mole) are stirred together and triethylamine (12.1 g., 0.12 mole) is added over a 15-minute period. The reaction is stirred for 2 hours, washed successively with 300 ml. portion of water, 5 percent sodium hydroxide solution, 5 percent hydrochloric acid solution and finally water. The dichloromethane layer is dried over magnesium sulfate, filtered and the solvent evaporated in vacuo. The solid product, N-(3-chlorobenzoyl)-N-methyltrifluoromethanesulfonamide, is recrystallized from benzene-hexane twice and dried to give white crystals, m.p. 57.5°–59° C.

Analysis:	% C	% H	% N
Calculated for $C_9H_7ClF_3NO_3S$:	35.8	2.3	4.6
Found:	36.0	2.4	4.7

The following compounds are prepared according to the procedure of example 2. In each case, the correspondingly substituted benzoyl chloride, and N-alkyl- or N-alkenyl trifluoromethylsulfonamide are used as reactants.

Compound	Boiling Point (in °C./mm.) or Melting Point (in °C.)
N-(2,4-dichlorobenzoyl)-N-methyltrifluoro methanesulfonamide	93/0.03
N-(4-chlorobenzoyl)-N-methyltrifluoromethane sulfonamide	47.5–49.5
N-(2-chlorobenzoyl)-N-methyltrifluoromethane sulfonamide	81/0.7
N-(3-methylbenzoyl)-N-methyltrifluoromethane sulfonamide	39.5–41.5
N-(2-acetoxybenzoyl)-N-methyltrifluoromethane sulfonamide	140/10[illegible]
N-(3,4,5-trimethoxybenzoyl)-N-methyltrifluoro methanesulfonamide	121–125
N-benzoyl-N-ethyltrifluoromethanesulfonamide	45.5–46.5
N-benzoyl-N-allyltrifluoromethanesulfonamide	81/0.08
N-(3-bromobenzoyl)-N-methyltrifluoromethane sulfonamide	67–68.5

What we claim is:

1. A compound of the formula:

wherein R' is cyclopropyl, lower alkyl or lower alkenyl. Ar is phenyl or naphthyl, Y is methylanlfonyl, lower alkyl, lower haloalkyl, lower alkoxy, phenyl, halogen, nitro, cyano or acetoxy and *n* is zero to three.

2. A compound according to claim 1 wherein R' is methyl.

3. A compound according to claim 1 wherein Ar is phenyl.

4. A compound according to claim 1 wherein R′ is methyl and Ar is phenyl.

5. A compound according to claim 4 wherein Y is methyl, trifluoromethyl, methoxy, phenyl, halogen, nitro, cyano or acetoxy.

6. The compound N-(3-bromobenzoyl)-N-methyl-trifluoromethanesulfonamide according to claim 1.

7. The compound N-(4-chlorobenzoyl)-N-methyl-trifluoromethanesulfonamide.

8. The compound N-(3-chlorobenzoyl)-N-methyl-trifluoromethanesulfonamide.

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 3,609,187 Dated September 28, 1971

Inventor(s) George G. I. Moore and Alvin C. Conway

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

Column 3, line 60, "98°-100bL C./20 mm." should read -- 98°-100° C./20 mm. --. Column 4, line 47 should be deleted. Line 48 should read -- N-(2,4-dichlorobenzoyl)-N-methyltrifluoro$_4$--. Column 4, line 54, "140/10^{-14}" should read -- 140/10^{-4} --. Column 4, line 71, "methylanlfonyl" should read -- methylsulfonyl --.

Signed and sealed this 2nd day of May 1972.

(SEAL)
Attest:

EDWARD M.FLETCHER, JR.
Attesting Officer

ROBERT GOTTSCHALK
Commissioner of Patents

ORM PO-1050 (10-69)

USCOMM-DC 60376-P69
U.S. GOVERNMENT PRINTING OFFICE : 1969 O—366-334