[54] **N-AROYL SULFONAMIDES**

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[*] Notice: The portion of the terms of this patent subsequent Sept. 28, 1988, has been disclaimed.

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

[22] Filed: **April 14, 1969**

[21] Appl. No.: **816,038**

[52] **U.S. Cl.**......**260/465 D,** 260/556 F, 260/294.8 F, 260/332.2 C, 260/347.2, 260/250 R, 260/545 R, 424/304, 424/321, 424/263, 424/275, 424/285, 424/250

[51] **Int. Cl.**..**C07c 143/74**

[58] **Field of Search**........................260/556 F, 465 D

[56] **References Cited**

UNITED STATES PATENTS

2,732,398	1/1956	Brice et al.	260/556 F
2,915,554	12/1959	Ahlbrecht et al	260/556 F

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[57] **ABSTRACT**

N-Aroylperfluoroalkanesulfonamides wherein the perfluoroalkane group is methyl or ethyl and the aryl group is phenyl, naphthyl, pyridyl, thienyl, furyl, or pyrazinyl, optionally substituted, and their pharmaceutically acceptable salts, are active anticonvulsant agents. Processes for the preparation of these compounds are described.

15 Claims, No Drawings

N-AROYL SULFONAMIDES

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to N-substituted perfluoroalkanesulfonamides and to compounds having anticonvulsant activity.

2. Prior Art

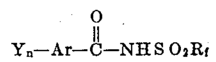
N-Substituted sulfonamides and N-substituted perfluoroalkanesulfonamides wherein the fluoroalkane chain is four to 12 carbon atoms are known to the art. U.S. Pat. No. 2,995,542 described compounds in which the nitrogen atom of the fluoroalkanesulfonamido group is substituted by a carbonyl carbon. However, the compounds described there are fluorocarbon acrylic-type sulfonamides. No prior disclosure of N-aroylperfluoroalkanesulfonamides or their physiological activity is known.

SUMMARY OF THE INVENTION

This invention relates to certain N-aroyl-substituted fluoroalkanesulfonamides, in which the aryl radical is selected from the group consisting on phenyl, naphthyl, pyridyl, thienyl, furyl and pyrazinyl, which may be substituted. The fluoroalkane group must contain one or two carbon atoms. Pharmaceutically acceptable salts of the compounds are also within the scope of the invention. Compositions containing the compounds of the invention and processes for their reparation are described. These compounds are active anticonvulsive agents.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to compounds of the formula



$$Y_n\text{—Ar—}\overset{\overset{O}{\|}}{C}\text{—NHSO}_2R_f$$

Formula I

wherein *n* is zero, one or two, Y is selected independently from the group consisting of lower alkyl, lower haloalkyl, lower alkoxy, phenyl, halogen, nitro, and cyano but Y may not occupy a position ortho to the carbonyl group except when Y is fluorine, or when Ar is phenyl, *n* is 2 and Y is chlorine and not more than one chlorine atom is in the ortho position; Ar is phenyl, naphthyl, pyridyl, thienyl, furyl or pyrazinyl and R_f is perfluoroalkyl of one or two carbon atoms; and pharmaceutically acceptable salts thereof.

The term "lower" when applied herein to alkyl, haloalkyl, alkoxy and alkylsulfonyl substituents signifies the presence of one to four carbon atoms; substituents having one carbon atom are preferred, because starting materials for such compounds are generally more readily available.

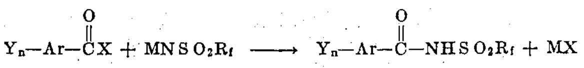
R_f is preferably trifluoromethyl, since the compounds containing this group have generally been somewhat more active as anticonvulsant agents. Compounds wherein R_f contains as many as four carbon atoms are inactive.

When the substituent Y occupies a position ortho to the carbonyl group of Formula I it has been observed that substituents other than fluorine generally result in reduced activity in the compounds of the present invention. No completely satisfactory theoretical explanation for this observation is known, although the steric bulk of the substituent is probably involved. However, one exception to this observation is the case of compounds having two chlorine atoms occupying positions on the aromatic ring, although both chlorine atoms may not be ortho.

The amido nitrogen of the compounds of Formula I bears a hydrogen which is relatively acidic. It may be replaced by metal ions by neutralization e.g., with a base or a salt of a weak acid to form salts of the compound. Suitable metal ions which may be utilized are preferably those which are pharmaceutically acceptable, for example sodium and potassium, when the compounds of the invention are to be used as anticonvulsants. Other pharmaceutically acceptable cations, which are well known to the art, may also be included in salts of the compounds of the invention.

The compounds of the invention are prepared conveniently by the reaction of an aroyl halide with a perfluoroalkanesulfonamide or its salt as shown in the following equation:

Equation I



$$Y_n\text{—Ar—}\overset{\overset{O}{\|}}{C}X + MNSO_2R_f \longrightarrow Y_n\text{—Ar—}\overset{\overset{O}{\|}}{C}\text{—NHSO}_2R_f + MX$$

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

The aroyl halides or their precursor acids and the perfluoroalkanesulfonamides and their salts used to prepare the compounds of this invention are known to the art, or are readily prepared by methods known to the art. Thus, the perfluoroalkanesulfonamides can be prepared as described in U. S. Pat. No. 2,732,398; aroyl halides are readily prepared by treating aromatic acids or anhydride with thionyl chloride.

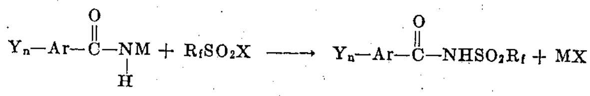
Aroyl anhydrides may be used in place of aroyl halides, although they are generally not preferred.

It is preferred that the reaction be run in the presence of base, although base is not essential, and a non-reactive solvent is preferred. Conveniently, this solvent is acetone, but other solvents including alkyl ketones, esters, mono- and diglyme, benzene, alkanes, chlorinated hydrocarbons 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 and N,N-dimethylaniline. 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 procedures to obtain dry conditions are apparent to those skilled in the art.

The reaction between the aroyl halide and the perfluoroalkanesulfonamide 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.

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 amide, or its salt, with a perfluoroalkanesulfonyl halide, as shown in the following equation



$$Y_n\text{—Ar—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}\underset{\underset{\displaystyle H}{|}}{N}M + R_fSO_2X \longrightarrow Y_n\text{—Ar—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—NHSO}_2R_f + MX$$

In the equation above Y, n, Ar, R_f, M and X are as defined previously hereinabove. However, this route is presently believed to be less desirable. Other routes such as the reaction of ketenes with perfluoroalkanesulfonamides are possible routes to the compounds of the invention.

For general use as anticonvulsants, the compounds of the present invention are preferably administered orally. For oral administration they are preferably administered as salts of pharmaceutically acceptable cations, as are well known to the art, and particularly as sodium salts. The compounds of the present invention are active as anticonvulsants, although it will be appreciated that some are more active than others.

The compounds of the invention are especially advantageous because the duration of their effect is quite long, often 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 specific does 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 this 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 compounds of Formula I or their pharmaceutically acceptable salts 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, electro-shock and chemically-induced shock. More specifically, antagonism of corneal supramaximal electroshock and 1,5-pentamethylene-tetrazole-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).

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 anti-shock 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 preferred compounds of the invention have been found to have a therapeutic index greater than 5.

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).

The preferred anticonvulsant compounds of the present invention include

N-(2-fluorobenzoyl)trifluoromethanesulfonamide
N-benzoyltrifluoromethanesulfonamide
N-(3-nitrobenzoyl)trifluoromethanesulfonamide
N-(3-trifluoromethylbenzoyl)trifluoromethanesulfonamide
N-(3-chlorobenzoyl)trifluoromethanesulfonamide
N-(3-fluorobenzoyl)trifluoromethanesulfonamide
N-(4-nitrobenzoyl)trifluoromethanesulfonamide
N-(2,4-dichlorobenzoyl)trifluoromethanesulfonamide
N-(4-chlorobenzoyl)trifluoromethanesulfonamide
N-(3-bromobenzoyl)trifluoromethanesulfonamide
N-(4-fluorobenzoyl)trifluoromethanesulfonamide
N-(3,4-dichlorobenzoyl)trifluoromethanesulfonamide

and the sodium salts of the above compounds. The preparation and use of these compounds for their anticonvulsant action appears to be the presently best known means for practicing the invention.

Certain compounds of this invention also show activity as insecticides, antimicrobial agents, diuretics, herbicides and plant growth modifiers. The herbicidal and plant growth modifying activity was determined using screening tests against experimental plantings. The compounds of this invention are useful as chemical intermediates.

The activity of these compounds is theorized to be the result of inhibition of the enzyme carbonic anhydrase. This 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, anti-glaucoma agents and in the facilitation of acclimatization to higher altitudes. Certain plant growth modifiers are known to be effective inhibitors of plant carbonic anhydrase.

In order to further illustrate the invention the following non-limiting examples are provided. Melting points are uncorrected.

EXAMPLE 1

N-Acylfluoroalkanesulfonamides: General Procedure, according to Equation I.

A mixture of fluoroalkanesulfonamide (0.1 mole), sodium carbonate (0.2 mole) and acetone (about 200 ml.) is stirred one or more hours under a nitrogen atmosphere. The co-reactant acid chloride (0.1 mole), diluted with a small amount of acetone, is added during one or more hours. A mild exotherm is sometimes observed. The reaction mixture is stirred under nitrogen for one or more hours, the mixture is filtered and the acetone is removed in vacuo. The product is a sodium salt, usually solid but sometimes a sticky gum. Dissolution in water, treatment with decolorizing charcoal and filtration may be used to partially purify the product. The product is reisolated by evaporation as the sodium salt, or acidification of the filtrate may be used to obtain the product compound of Formula I. Some of these compounds of Formula I have an appreciable water solubility. Recrystallization of compounds is usually carried out from trichloroethylene, or mixtures of aromatic and aliphatic hydro-carbons such as benzene-hexane. Sublimation may also be used as a purification technique. Sodium salts of the compounds are successfully recrystallized from nitromethane.

EXAMPLE 2

Trifluoromethanesulfonamide (9.1 g., 0.06 mole), sodium carbonate (12.9 g., 0.12 mole) and acetone (250 ml.) are stirred for four hours. 4-Cyanobenzoyl chloride (10.1 g., 0.061 mole) is added and the solution is stirred overnight. The solution is filtered and the acetone is evaporated in vacuo. Water is added to dissolve the crude product and the solution is filtered, then acidified to precipitate the product. The suspension is extracted with dichloromethane, the extracts are dried over magnesium sulfate, filtered, and the solvent is removed in vacuo. The product is purified by sublimation at 130° C./0.03 mm. to yield a white solid, N-4-(cyanobenzoyl)trifluoromethanesulfonamide, m.p. 148°–150° C.

Analysis	% C	% H	% N
calculated for $C_9H_5F_3N_2O_3S$:	38.8	1.8	10.1
Found:	38.9	1.8	10.2

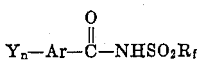
The following compounds are prepared from trifluoromethane — or trifluoroethane sulfonamide and appropriately substituted aroyl halides, according to the procedure of Example 1.

Example No.	Compound	Melting point (in °C.)
3	N-benzoyltrifluoromethanesulfonamide	112.5–114.5
4	N-(2-fluorobenzoyl)trifluoromethanesulfonamide	62–64
5	N-(3-nitrobenzoyl)trifluoromethanesulfonamide	145–152
6	N-(3-trifluoromethylbenzoyl)-trifluoromethanesulfonamide	148–149.5
7	N-(3-bromobenzoyl)trifluoromethanesulfonamide	134–135
8	N-(3-chlorobenzoyl)trifluoromethanesulfonamide	118–119.5
9	N-(3-fluorobenzoyl)trifluoromethanesulfonamide	129.5–131
10	N-(4-nitrobenzoyl)trifluoromethanesulfonamide	140–145
11	N-(4-chlorobenzoyl)trifluoromethanesulfonamide	156.5–158
12	N-(4-fluorobenzoyl)trifluoromethanesulfonamide	148–150
13	N-(3,4-dichlorobenzoyl)-trifluoromethanesulfonamide	167–168.5
14	Sodium N-(2,4-dichlorobenzoyl)trifluoromethanesulfonamide	218–220 d.
15	N-(2-naphthoyl)trifluoromethanesulfonamide	149–151
16	N-(p-biphenylcarbonyl)trifluoromethanesulfonamide	176–178
17	N-(4-methoxybenzoyl)-trifluoromethanesulfonamide	112–114
18	N-(3-methylbenzoyl)-trifluoromethanesulfonamide	134–136
19	N-benzoylperfluoroethanesulfonamide	115–117.5
20*	Triethylammonium N-(4-nitrobenzoyl)-trifluoromethanesulfonamide	101.5–105
21	Sodium N-(3-nicotinyl)-trifluoromethanesulfonamide	361–364 d.
22	N-(2-thenoyl)-trifluoromethanesulfonamide	128–130
23	N-(2-furoyl)-trifluoromethanesulfonamide	130–131.5
24	Sodium N-pyrazinecarbonyl-trifluoromethanesulfonamide	366–367

*Prepared using triethylamine as base in place of sodium carbonate.

WHAT IS CLAIMED IS:

1. A compound of the group consisting of acidic compounds of the formula



$$Y_n\text{—Ar—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—NHSO}_2R_f$$

wherein *n* is zero, one or two, Y is selected independently from the group consisting of lower alkyl, lower haloalkyl, lower alkoxy, phenyl, halogen, nitro and cyano but Y may not occupy a position ortho to the carbonyl group except when Y is fluorine or when Ar is phenyl, *n* is two and Y is chlorine, and not more than one chlorine atom may occupy the ortho position, Ar is phenyl or naphthyl and R_f is perfluoroalkyl of one or two carbon atoms; and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein R_f is trifluoromethyl and Ar is phenyl.

3. The compound sodium N-(2,4-dichlorobenzoyl)trifluoromethanesulfonamide according to claim 1.

4. The compound N-(3-chlorobenzoyl)trifluoromethanesulfonamide according to claim 1.

5. The compound N-(4-chlorobenzoyl)trifluoromethanesulfonamide according to claim 1.

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

7. The compound N-(2-fluorobenzoyl)trifluoromethanesulfonamide according to claim 1.

8. The compound N-(3-nitrobenzoyl)trifluoromethanesulfonamide according to claim 1.

9. The compound N-(3-trifluoromethylbenzoyl)trifluoromethane-sulfonamide according to claim 1.

10. The compound N-(3-fluorobenzoyl)trifluoromethanesulfonamide according to claim 1.

11. The compound N-(4-nitrobenzoyl)trifluoromethanesulfonamide according to claim 1.

12. The compound N-(4-fluorobenzoyl)trifluoromethanesulfonamide according to claim 1.

13. The compound N-(4-cyanobenzoyl)trifluoromethanesulfonamide according to claim 1.

14. The compound N-(p-biphenylcarbonyl)trifluoromethanesulfonamide according to claim 1.

15. The compound N-(3,4-dichlorobenzoyl)trifluoromethanesulfonamide according to claim 1.

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