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3,661,990

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3,661,990

N-ALKYLSULFONYL BENZOYLHALOALKYL-SULFONANILIDES

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Int. Cl. C07c *143/74*

U.S. Cl. 260—556 F 11 Claims

ABSTRACT OF THE DISCLOSURE

N-alkylsulfonyl benzoylhaloalkylsulfonalides in which the aromtaic rings are optionally substituted. These compounds are active anti-inflammatory agents.

This invention relates to N-alkylsulfonyl benzoylhaloalkylsulfonanilides in which the aromatic rings are optionally substituted. These compounds are active anti-inflammatory agents and some also are analgesic, antipyretic and anti-microbial agents.

It is an object of the invention to provide compounds which are anti-inflammatory agents.

It is another object of the invention to provide compounds for the control of microbes.

It is another object of the invention to provide compounds which are analgesic agents.

It is another object of the invention to provide compounds which are anti-pyretic agents.

It is a further object of the invention to provide a method for controlling inflammation in mammalian tissue.

It is a further object of the invention to provide a method for releaving pain.

It is still another object of the invention to provide anti-inflammatory compositions containing one or more N-alkylsulfonyl benzoylhaloalkylsulfonanilides as active ingredients therein.

It is still another object of the invention to provide anti-microbial compositions containing one or more N-alkylsulfonyl benzoylhaloalkylsulfonanilides as active ingredients therein.

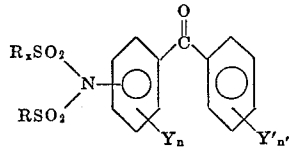
It is still another object of the invention to provide analgesic compositions contaning one or more N-alkylsulfonyl benzoylhaloalkylsulfonanilides as active ingredients therein.

It is still another object of the invention to provide antipyretic composititon containing one or more N-alkylsulfonyl benzoylhaloalkylsulfonanilides as active ingredients therein.

Still other objects will be made apparent by the following specification.

DETAILED DESCRIPTION

According to the present invention, there is provided a class of compounds of the formula:



I

wherein R is alkyl or haloalkyl of one to four carbon atoms and R_x is chloromethyl or fluoroalkyl of one to four carbon atoms, the fluoroalkyl radical having at least one fluorine atom bonded to the alpha carbon atom or at least two fluorine atoms bonded to a beta carbon atom, Y and Y' are the same or different and are selected from hydroxy, halogen, lower alkyl, lower haloalkyl, lower alkoxy and lower haloalkoxy, and *n* and *n'* are the same or different and are zero to three.

The term lower when applied to substituent groups (radicals) of this invention, such as alkyl, haloalkyl, alkoxy and haloalkoxy, refers to groups containing one to about four carbon atoms.

When R_x is fluoroalkyl, it can be straight or branched chain perfluoroalkyl or partially fluorinated alkyl, and it can contain chlorine. When R_x is fluoroalkyl, it preferably has at least two fluorines bonded to the alpha carbon atom, or one fluorine bonded to the alpha carbon atom and at least two fluorines bonded to the beta carbon atom. When *n* is zero, the ring adjacent to the alkylsulfonamido groups is unsubstituted except for that group and the benzoyl group. Similarly, when *n'* is zero, the second ring is unsubstituted except for the group shown in the formula and attached thereto through the carbonyl link.

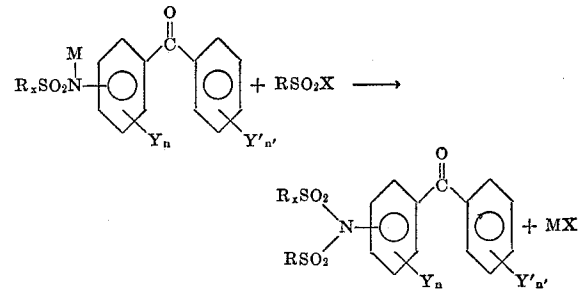
The compounds of the invention are generally active as anti-inflammatory agents. The compounds in which R_x is fluoroalkyl containing one or two carbon atoms are preferred, since such compounds are usually more active, and compounds wherein R_x is trifluoromethyl or difluoromethyl are most preferred. When R_x contains but one carbon atom, R is preferably alkyl rather than haloalkyl.

Compounds of the invention wherein R is alkyl or haloalkyl of one or two carbon atoms are preferred, because as the number of carbon atoms in R increases, anti-inflammatory activity decreases. When R is haloalkyl, halogen is fluorine or chlorine. Compounds wherein R is is methyl, ethyl, fluoromethyl or chloromethyl are most preferred.

The radicals R_x and R may contain only fluorine or chlorine, or these halogens may both be present in one radical, or the two radicals may contain different halogens.

Compounds of the invention wherein the sulfonylsulfonamide group is oriented meta to the carbonyl of the benzophenone group are preferred.

The compounds of the present invention are prepared according to the following reaction



wherein R_x, R, Y, Y', *n* and *n'* are as defined hereinabove, M is a cation, e.g. of alkali metals, alkaline earth metals, amines or aluminum and X is halogen (preferably chlorine or fluorine, or the residue of an anhydride grouping, i.e. $—OSO_2R$). R_x and R may also be reversed in the foregoing equation.

Compounds wherein R_x contains one or two carbon atoms and is identical with R (i.e. both are haloalkyl) are optionally prepared by reacting at least two equivalents of the appropriate haloalkylsulfonyl halide or anhydride with an aminobenzophenone of Formula IV, described hereinafter.

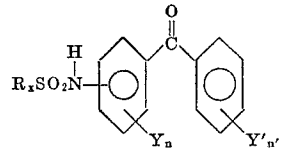
A non-reactive organic solvent, preferably one in which the salts of Formula II have some solubility, is used, such as 1,2-dimethoxyethane, diethyl ether, diisopropyl ether, acetone, chloroform, dichloromethane and the like.

The reaction temperature may vary, from the freezing point to the boiling point of the solvent used, depending upon the reactivity of the intermediate compound of Formula II and the sulfonyl halide or anhydride. In some cases the reaction proceeds at the reflux temperature of

the solvent, while in others ice bath or room temperature is satisfactory.

The reaction product is generally isolated by filtration to remove the salt MX which is formed as a byproduct, followed by evaporation of the solvent. The product is dissolved in an organic solvent such as chloroform, dichloromethane, diethyl ether and the like and washed with water and base to remove impurities such as unreacted starting material and inorganic salts. The solution is dried, solvent removed in vacuo and the residue is further purified, if necessary, by conventional techniques. Usually recrystallization from ethanol or ethanol-water mixtures is satisfactory.

The salts of Formula II are prepared from the corresponding acid form compound

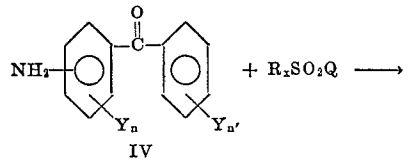


III

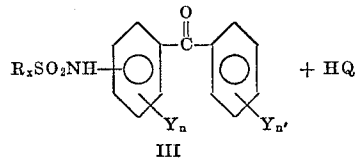
by adding the stoichiometric amount of a base in inert solvent solution (aqueous or nonaqueous) to the acidic compound (III). The resulting solution is treated to remove the solvent, e.g. by evaporation under reduced pressure to obtain the salt, usually as a dry powder. Appropriate bases for use in preparing the metal salts include metal oxides, carbonates, bicarbonates and alkoxides. Compounds of Formula II wherein M is aluminum, alkali metals, alkaline earth metals and amines are prepared in this way. Compounds wherein M is sodium are generally preferred because they are readily available and relatively inexpensive.

Alternatively, the salts may be preformed in situ by use of metal hydrides such as sodium hydride in an inert solvent or a base such as potassium carbonate, sodium hydroxide and the like in aprotic or protic solvents.

The acid form compounds (III) are prepared by condensing an aminobenzophenone with a haloalkylsulfonyl halide or anhydride according to the following scheme:



IV



III

wherein R_x, n, n', Y and Y' are as previously defined and Q represents a halogen atom, preferably chlorine or fluorine, or the corresponding anhydride grouping

$$-OSO_2R_x$$

(R_x being defined as above). Approximately equivalent amounts of the reactants are brought together at temperatures most often ranging between about −15 and 150° C. If necessary or desirable, the reaction can be carried out in a pressure vessel. The reaction is preferably, but not necessarily, carried out in the presence of an acid acceptor such as the alkali or alkaline earth metal carbonates and bicarbonates or a teritary amine such as pyridine, triethylamine or N,N-dimethylaniline. The amount of the acid acceptor can be varied widely; however, a 10 mole percent excess of that amount of base sufficient to bind the liberated strong acid (HQ) is routinely employed.

The condensation is usually conducted in the presence of an appropriate inert organic solvent. Typical solvents suitable for this purpose are methylene chloride, chloroform, carbon tetrachloride, benzene, toluene, bis(2-methoxyethyl) ether, N,N-dimethylformamide, 1,2-dimethoxyethane and the like.

After reaction is complete, if the reaction solvent is not water miscible, the production mixture can be extracted with a dilute aqueous base solution. The product, in the form of a salt which is usually soluble in the aqueous layer, is precipitated therefrom by addition of a mineral acid such as hydrochloric or sulfuric acid, and collected. Alternatively, the product mixture can be washed with aqueous hydrochloric acid, the solvent evaporated in vacuo, and the residue dissolved in a dilute aqueous base solution which is washed with dichloromethane and treated with decolorizing charcoal. The product, in the form of a salt, is then isolated as described above.

If the reaction solvent is water miscible, the product is generally obtained by dilution of the reaction mixture with water. The product, a solid or oil, is separated and purified by conventional methods. The compounds prepared according to the foregoing procedures are generally crystalline solids purified, in general, by recrystallization from aqueous alcohol, trichloroethylene, hexane, benzene-hexane mixtures and the like. Elution chromatography has also been found to be a useful purification technique.

Suitable haloalkanesulfonylanhydrides and halides (e.g. chlorides and fluorides) for use as starting materials in these procedures are known to the art, for example:

fluoromethanesulfonyl chloride,
fluorochloromethanesulfonyl chloride,
difluoromethanesulfonyl chloride,
chloromethanesulfonyl chloride,
trifluoromethanesulfonic anhydride,
2,2,2-trifluoroethanesulfonyl chloride,
trifluoromethanesulfonyl chloride,
1,1,2,2-tetrafluoroethanesulfonyl chloride,
2,2,3,3-tetrafluoropropanesulfonyl chloride,
2-hydroperfluoropropanesulfonyl chloride,

and many others disclosed, e.g., in U.S. Pat. 2,732,398.

Most of the aminobenzophenones, IV, are described in the general chemical literature or can be prepared from corresponding known substituted nitrobenzophenones by reduction. All of the nitrobenzophenones or aminobenzophenones not specifically disclosed in the chemical literature are prepared by methods known in the literature for analogous compounds. Exemplary of such starting materials are:

5-amino-2-chlorobenzophenone,
3-amino-4'-fluorobenzophenone,
3-amino-5-bromobenzophenone,
3-amino-4'-ethylbenzophenone,
3-amino-2'-ethoxybenzophenone,
3-amino-4'-ethoxybenzophenone, etc.

In some cases intermediates of Formula II are preferably prepared from other intermediates of Formula II. For example, 3-benzoyl-4-hydroxytrifluoromethanesulfonanilide may be prepared by reaction of 3-benzoyl-4-methoxytrifluoromethanesulfonanilide with hydroiodic acid in acetic acid.

As noted previously, the compounds of the invention are as a class active anti-inflammatory agents, although some are more active than others. The anti-inflammatory activity can be conveniently demonstrated using assays designed to test the ability of these compounds to antagonize the local edema which is a characteristic of the anti-inflammatory response (rat foot edema test) and to inhibit the onset of the erythematous manifestation of inflammation (guinea pig erythema test).

These are standard assays well known to those skilled in the art. They are described in journals and other publications. Leading references to the rat foot edema test are:

(1) Adamkiewicz et al., Canad. J. Biochem. Physio., 33: 332, 1955;

(2) Selye, Brit. Med. J., 2:1129, 1949; and
(3) Winter, Proc. Soc. Exper. Biol. Med., 111:544, 1962.

Leading references to the guinea pig erythema test are:

(1) Wilhelmi, Schweiz. Med. Wschr., 79:577, 1949; and
(2) Winder et al., Arch. Int. Pharmacodyn, 116:261, 1958.

Other standard assays well-known to those skilled in the art may also be used to detect anti-inflammatory activity in the compounds of the present invention, for example, the cotton pellet granuloma test or the adjuvant arthritis test.

Preferred compounds of the invention because of very high anti-inflammatory activity are:

N-methylsulfonyl-3-benzoyltrifluoromethanesulfonanilide,
N-fluoromethylsulfonyl-3-benzoyltrifluoromethanesulfonanilide,
N-chloromethylsulfonyl-3-benzoyltrifluoromethanesulfonanilide, and
N-trifluoromethyl-3-benzoyltrifluoromethanesulfonanilide.

The compounds of the invention are preferably administered orally, for example, as four percent acacia suspensions, but also may be administered parenterally. Amounts are generally about 1 to 500 mg./kg. of body weight of the mammal to be treated.

Many of the compounds of the invention are active as anti-microbial agents according to standard anti-microbial assays. Specifically, the anti-microbial activity of the compounds of the invention has been evaluated using a variation of the original agar-plate diffusion method of Vincent and Vincent (e.g., see Vincent, J. G., and Vincent, Helen W., Proc. Soc. Exptl. Biol. Med., 55:162–164, 1944, and Davis, B. D., and Mingioli, E. S., Jour. Bact., 66:129–136, 1953).

The following examples are given for the purpose of further illustrating the procedures of the present invention, but are not intended in any way to be limiting on the scope thereof.

All melting points in the examples are uncorrected. The boiling points and melting points are given in degrees centigrade and the pressures in millimeters of mercury.

EXAMPLE 1

Intermediate compounds corresponding to Formula III are prepared according to the following general procedure:

In a three-necked round-bottomed flask equipped with a magnetic stirrer, a reflux condenser, a thermometer and an addition funnel are placed a substituted aminobenzophenone (30 mmoles), chloroform (50 ml.) and N,N-dimethylaniline (33 mmoles). To this stirred mixture a haloalkanesulfonic anhydride or haloalkanesulfonyl chloride (about 30 mmoles) is added dropwise at such a rate that the reaction temperature does not exceed 45° C. The mixture is then stirred two hours at ambient temperature. The mixture is washed with five percent hydrochloric acid, then the solvent is removed in vacuo. The residue is taken up in five percent aqueous sodium hydroxide and washed with dichloromethane. The basic aqueous phase is then heated on a steam bath, treated with decolorizing charcoal and acidified with concentrated hydrochloric acid. This mixture is then extracted with dichloromethane, and the extracts dried over magnesium sulfate. The solvent is removed in vacuo, and the product purified by recrystallization or (usually) column chromatography followed by recrystallization, usually from saturated hydrocarbons or mixtures of benzene and saturated hydrocarbons.

Representative compounds prepared according to this procedure as intermediates are as follows.

Compound:	Melting point, degrees
3-benzoyldifluoromethanesulfonanilide	99–100.5
3-benzoylfluoromethanesulfonanilide	117–120
3-(4-chloro-2-methylbenzoyl)trifluoromethanesulfonanilide	135–137
3-(4-methylbenzoyl)fluoromethanesulfonanilide	118–120
3-(4-chlorobenzoyl)difluoromethanesulfonanilide	127–129
3-benzoyl-2,2,2-trifluoroethanesulfonanilide	105.5–107
3-(4-methoxybenzoyl)difluoromethanesulfonanilide	118–120
3-(4-methoxybenzoyl)fluoromethanesulfonanilide	116.5–118.5
4-benzoyldifluoromethanesulfonanilide	124.5–126.5
3-benzoyltrifluoromethanesulfonanilide	99–101
4-benzoyltrifluoromethanesulfonanilide	136–137
3-(4-methylbenzoyl)trifluoromethanesulfonanilide	129.5–131.5
3-(4-methoxybenzoyl)trifluoromethanesulfonanilide	122.5–124.5
3-(4-chlorobenzoyl)trifluoromethanesulfonanilide	123.5–125.5
3-(3-chlorobenzoyl)trifluoromethanesulfonanilide	101–102
3-(2-chlorobenzoyl)trifluoromethanesulfonanilide	72–74
3-(2-methylbenzoyl)trifluoromethanesulfonanilide	92–93
3-benzoylperfluoroethanesulfonanilide	95–97
3-(4-fluorobenzoyl)trifluoromethanesulfonanilide	134–136
3-benzoyl-4-chlorotrifluoromethanesulfonanilide	106–108
3-benzoyl-(2-hydroperfluoroethane)sulfonanilide	80–80.5
3-benzoyl-4-chlorodifluoromethanesulfonanilide	99–102
4-chloro-3-(4-chlorobenzoyl)trifluoromethanesulfonanilide	82–83
4-chloro-3-(4-fluorobenzoyl)trifluoromethanesulfonanilide	133–134
3-(4-fluorobenzoyl)difluoromethanesulfonanilide	80–84
3-benzoylchloromethanesulfonanilide	95–97
4-chloro-3-(4-fluorobenzoyl)difluoromethanesulfonanilide	101–103
4-chloro-3-(4-chlorobenzoyl)difluoromethanesulfonanilide	81–83
3-(3-trifluoromethylbenzoyl)trifluoromethanesulfonanilide	86–88
3-benzoylperfluoro-n-butanesulfonanilide, B.P. 186° C./0.09 mm.	

The following intermediate compounds are prepared by hydroiodic acid-acetic acid cleavage of the corresponding methoxy derivatives:

3-benzoyl-4-hydroxytrifluoromethanesulfonanilide, M.P. 133–136°, and
3-(2-hydroxybenzoyltrifluoromethanesulfonanilide), M.P. 131–133°.

EXAMPLE 2

The following is exemplary of the preparation of the salts of Formula II.

To a solution of 12.21 g. of reagent grade sodium hydroxide (0.305 mole) in 300 ml. of water are added 95 g. of 3-benzoyldifluoromethanesulfonanilide (0.305 mole). The mixture is stirred until dissolution is complete and the solution has a pH of 7.2 (sensitive pH paper).

Water is removed to give a yellow solid which is taken up in about 200 ml. of glyme and treated with activated charcoal. The clear solution is then added dropwise with vigorous stirring to 5 liters of ethyl ether. The crystalline salt is isolated by filtration, washed with 4 liters of ethyl ether and dried to give the pure product, M.P. (dec.) 235° C.

Analysis.—Calculated for $C_{14}H_{10}F_2NaNO_3S$ (percent): C, 50.45; H, 3.05. Found (percent): C, 50.6; H, 3.2.

The following salts are prepared using the general method of Example 2:

potassium 3-benzoyltrifluoromethanesulfonanilide
lithium 3-benzoyltrifluoromethanesulfonanilide
dimethyl-2-hydroxyethylammonium 3-benzoyltrifluoromethanesulfonanilide
triethylammonium 3-benzoyltrifluoromethanesulfonanilide
chlorine salt of 3-benzoyltrifluoromethanesulfonanilide.

EXAMPLE 3

The compounds of the invention (Formula I) are prepared according to the following general procedure:

In a three-necked round-bottom flask equipped with a magnetic stirrer, a reflux condenser and an addition funnel is placed a salt of a haloalkylsulfonamidobenzophenone of Formula II (30 millimoles) in acetone (200 ml.) or other suitable solvent. To this stirred mixture is added a compound of the formula RSO_2X, wherein R and X are as previously defined (about 30 millimoles). The mixture is stirred at room temperature for at least one hour, although longer reaction times and higher temperatures may increase yields or initiate sluggish reactions. The solution is filtered then the solvent is removed in vacuo, and the residue is dissolved in dichloromethane or other suitable water-immiscible organic solvents, then washed with water and base. The product is recovered by evaporation of the solvent and recrystallized, sublimed, distilled or chromatographed if further purification is desired.

Representative compounds prepared according to this procedure are listed below:

Compound:	Melting point, degrees
N-fluoromethylsulfonyl - 3 - benzoyltrifluoromethanesulfonanilide	[1] 98.5–100.5
N-methylsulfonyl - 3 - benzoyltrifluoromethanesulfonanilide	108–110
N - trifluoromethylsulfonyl-3-benzoyltrifluoromethanesulfonanilide	68.5–70.5
N-chloromethylsulfonyl - 3 - benzoyltrifluoromethanesulfonanilide	110–112
N - n - butylsulfonyl - 3 - benzoyltrifluoromethanesulfonanilide	81–84

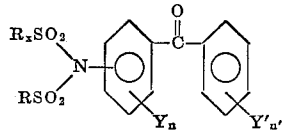
[1] *Analysis.*—Calculated for $C_{15}H_{11}F_4NO_3S_2$ (percent): C, 42.3; H, 2.6; N, 3.3. Found (percent): C, 42.6; H, 2.7; N, 3.3.

Additional compounds of the invention prepared by the preceding methods are as follows:

N-methylsulfonyl-3-benzoyldifluoromethanesulfonanilide
N-methylsulfonyl-3-benzoylfluoromethanesulfonanilide
N-fluoromethylsulfonyl-3-(4-chloro-2-methylbenzoyl)trifluoromethanesulfonanilide
N-methylsulfonyl-3-(4-methylbenzoyl)fluoromethanesulfonanilide
N-methylsulfonyl-3-(4-chlorobenzoyl)difluoromethanesulfonanilide
N-methylsulfonyl-3-benzoyl-2,2,2-trifluoromethanesulfonanilide
N-methylsulfonyl-3-(4-methoxybenzoyl)difluoromethanesulfonanilide
N-methylsulfonyl-3-(4-methoxybenzoyl)fluoromethanesulfonanilide
N-methylsulfonyl-4-benzoyldifluoromethanesulfonanilide
N-chloromethylsulfonyl-4-benzoyltrifluoromethanesulfonanilide
N-fluoromethylsulfonyl-3-(4-methylbenzoyl)-trifluoromethanesulfonanilide
N-fluoromethylsulfonyl-3-(4-methoxybenzoyl)-trifluoromethanesulfonanilide
N-fluoromethylsulfonyl-3-(4-chlorobenzoyl)-trifluoromethanesulfonanilide
N-fluoromethylsulfonyl-3-(3-chlorobenzoyl)trifluoromethanesulfonanilide
N-fluoromethylsulfonyl-3-(2-methylbenzoyl)trifluoromethanesulfonanilide
N-fluoromethylsulfonyl-3-benzoylperfluoromethanesulfonanilide
N-fluoromethylsulfonyl-3-(4-fluorobenzoyl)-trifluoromethanesulfonanilide
N-fluoromethylsulfonyl-3-benzoyl-4-chlorotrifluoromethanesulfonanilide
N-fluoromethylsulfonyl-3-benzoyl-(2-hydroperfluoroethane)sulfonanilide
N-methylsulfonyl-3-benzoyl-4-chlorodifluoromethanesulfonanilide
N-methylsulfonyl-4-chloro-3-(4-chlorobenzoyl)-trifluoromethanesulfonanilide
N-methylsulfonyl-4-chloro-3-(4-fluorobenzoyl)-trifluoromethanesulfonanilide
N-methylsulfonyl-3-(4-fluorobenzoyl)difluoromethanesulfonanilide
N-methylsulfonyl-3-benzoylchloromethanesulfonanilide
N-ethylsulfonyl-4-chloro-3-(4-fluorobenzoyl)-difluoromethanesulfonanilide
N-methylsulfonyl-4-chloro-3-(4-chlorobenzoyl)-difluoromethanesulfonanilide
N-methylsulfonyl-3-(3-trifluoromethylbenzoyl)-trifluoromethanesulfonanilide
N-methylsulfonyl-3-benzoylperfluoro-n-butanesulfonanilide

What is claimed is:

1. A compound of the formula



wherein R is alkyl or haloalkyl of one to four carbon atoms and R_X is chloromethyl, fluoroalkyl, or chlorofluoroalkyl wherein the alkyl groups have one to four carbon atoms, the fluoroalkyl or chlorofluoroalkyl radicals having at least one fluorine atom bonded to the alpha carbon atom or at least two fluorine atoms bonded to a meta carbon atom, Y and Y′ are the same or different and are selected from hydroxy, halogen, lower alkyl, lower haloalkyl, lower alkoxy and lower haloalkoxy, and *n* and *n′* are the same or different and are zero to three.

2. A compound according to claim **1** wherein *n* and *n′* are zero.

3. A compound according to claim **1** wherein R_X is trifluoromethyl.

4. A compound according to claim **1** wherein the nitrogen atom and the carbonyl group of the formula are oriented meta to one another.

5. A compound according to claim **4** wherein R and R_X each contain only one carbon atom.

6. N-methylsulfonyl-3 - benzoyltrifluoromethanesulfonanilide according to claim **1.**

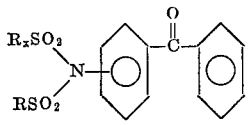
7. N - fluoromethylsulfonyl-3-benzoyltrifluoromethanesulfonanilide according to claim **1.**

8. N-trifluoromethylsulfonyl - 3 - benzoyltrifluoromethanesulfonanilide according to claim **1.**

9. N-n-butylsulfonyl - 3-benzoyltrifluoromethanesulfonanilide according to claim **1.**

10. N-chloromethylsulfonyl-3-benzoyltrifluoromethanesulfonanilide according to claim 1.

11. A compound of the formula



wherein R is methyl or halomethyl and R_x is chloromethyl or a fluoromethyl containing at least one fluorine atom.

References Cited

UNITED STATES PATENTS

3,576,866 4/1971 Robertson et al. ____ 260—556 F

HENRY R. JILES, Primary Examiner

S. D. WINTERS, Assistant Examiner

U.S. Cl. X.R.

260—556 SN, 556 A, 570 A, 543 R; 424—321

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,661,990 Dated May 9, 1972

Inventor(s) Joseph Kenneth Harrington

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

Column 1, line 43, "contaning" should be --containing--

Column 2, line 28, "R is is methyl," should be --R is methyl,--

Column 2, line 45, "II" should be inserted under the formula

Column 3, line 68, "teritary" should be --tertiary--

Column 4, line 5, "production" should be --product--

Column 7, line 25, "In" should be --Into--

Column 7, line 70, "trifluoromethane-" should be --trifluoroethane- --

Column 8, line 15, "benzoylperfluoromethane-" should be --benzoylperfluoroethane- --

Column 8, line 54, "meta" should be --beta--

Signed and sealed this 1st day of May 1973.

(SEAL)
Attest:

EDWARD M. FLETCHER, JR.
Attesting Officer

ROBERT GOTTSCHALK
Commissioner of Patents

FORM PO-1050 (10-69)

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