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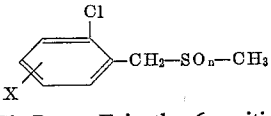
2,4- and 2,6-DIHALOBENZYL METHYL SULFOXIDES AND SULFONES

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U.S. Cl. 260—607 11 Claims

ABSTRACT OF THE DISCLOSURE

2,4- or 2,6-dihalobenzyl methyl sulfoxides and the corresponding sulfones of the formula



wherein X is Cl, Br or F in the 6-position or Cl in the 4-position and $n=1$ or 2 are effective anti-inflammatory agents.

The present invention relates to novel compounds useful as anti-inflammatory agents. More concretely stated, the invention concerns as series of 2,4- and 2,6-dihalo-benzyl methyl sulfoxides and a series of the corresponding 2,4- and 2,6-dihalo-benzyl methyl sulfones.

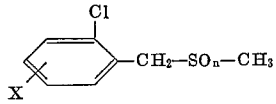
Inflammation in its various manifestations represents one of the serious problems in the clinical field. Although it is known that many diseases may be engendered thereby, clinical physicians have often encountered difficulties in eliminating inflammation in the therapy of various diseases. Prompt removal of inflammation or prevention of the occurrence thereof is very important for shortening the term of disease and for removing pain as quickly as possible. Many attempts have been made to provide anti-inflammatory agents suitable for these purposes.

Present anti-inflammatory agents can be divided into two groups; (a) steroidal anti-inflammatory agents, i.e.

adrenocortical hormones such as prednisolone, triamcinoline, hydrocortisone, dexamethasone, or the like, and (b) non-steroidal anti-inflammatory agents which consist mainly of pyrazolidine derivatives such as phenylbutazone, oxyphenbutazone, 1,4-diphenyl-3,5-dioxopyrazolidine, aminopyrine, and the like, salicyclic acid derivatives such as acetyl salicyclic acid, and the like, and—more recently—dimethylsulfoxide.

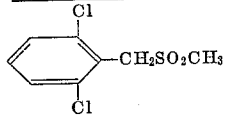
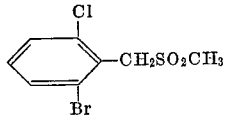
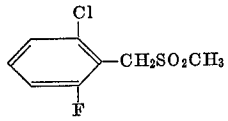
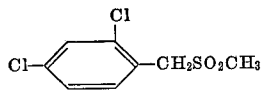
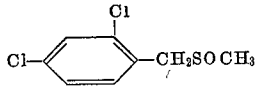
However, those of the former group provoke hypofunction of the anterior pituitary gland and adrenal cortex when they are used for a slightly prolonged period. Once such phenomena occur to a patient, administration of such steroidal anti-inflammatory agents must continue throughout his life. On the other hand, those of the second group are often accompanied by undesirable side effect on elements of the digestive system such as stomach, intestinal canal, etc. and often disturb the normal functions of kidney, liver, heart, etc. Therefore, both groups of anti-inflammatory agents necessitate careful administration to patients, especially to those whole illness involves any hormonic and metabolic mechanism and/or functions of their viscera such as stomach, intestinal canal, kidney, liver, heart, etc. Accordingly, debut of an anti-inflammatory agent which is safely administrable to patients in a wide field of inflammatory conditions has long been a desideratum in the art.

According to the present invention, a series of novel non-steroidal 2,4- and 2,6-dihalo-benzyl methyl sulfoxides and the corresponding sulfones of the formula

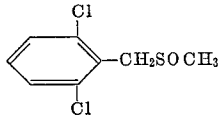
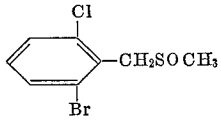
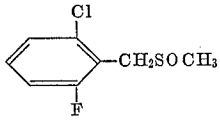
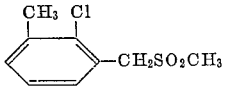
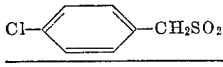
 (I)

wherein X stands for Cl, Br or F attached to the 6-position, or Cl attached to the 4-position, and n is 1 or 2, having an effective anti-inflammatory activtity, is provided.

These novel compounds of Formula I show an effective anti-inflammatory activity with a lower toxicity than hitherto-known non-steroidal anti-inflammatory agents. Detailed animal experimental data on the said anti-inflammatory action are shown in the following table:

Compound	Anti-inflammatory action [1] Dose, mg./k.	Inhibition, percent	Probability, percent	LD_{50} mg./kg.[2]
	25	44.6	<0.01	500–1,000
	100	49.8	<0.01	250–500
	12.5	58.6	<0.01	250
	100	51.7	<0.01	1,000
	25	40.4	<0.05	250–500

See footnotes at end of table.

Compound	Anti-inflammatory action [1] Dose, mg./k.	Inhibition, percent	Probability, percent	LD_{50} mg./kg.[2]
	50	50.0	<0.01	250-500
	25	32.8	<0.05	250-500
	12.5	40.6	<0.01	250
Acetyl salicylic acid	200	48.9	<0.01	600
Phenylbutazone	100	46.3	<0.01	340
	200	7.6	(3)	1,000
	300	29.1	<0.05	>1,000

[1] Anti-inflammatory action was measured by oral administration in rats with the method of carrageenin edema (Proc. Soc. Exp. Biol. Med. III, 544 (1962)).
[2] The median lethal dose (LD_{50}) was measured by intraperitoneal administration in mice.
[3] Not significant.

Furthermore, compounds (I) show no such side effects as often accompany steroidal compounds, and show far less side effects than hitherto-known non-steroidal anti-inflammatory agents.

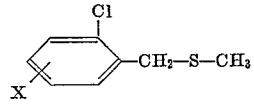
The present compounds (I) also exhibit an analgetic action, and an inhibitory effect against pulmonary (lung) affections due to influenza virus, etc.

It is one object of the present invention to provide such valuable and novel 2,4- and 2,6-dihalo-benzyl methyl sulfoxides and sulfones (I) which are useful as anti-inflammatory agents.

A further object is to provide new pharmaceutical compositions containing a compound or compounds (I).

Other objects of the present invention and advantageous features thereof will become apparent as the description proceeds.

These compounds (I) can be prepared by, for example, subjecting the compounds of the formula


(II)

wherein X has the same meaning as above, to oxidation.

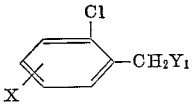
For the purposes of the oxidation, such conventional oxidizing agents may be employed as, for example, hydrogen peroxide, manganese dioxide, nitric acid, chromic acid, chromic anhydride, lead tetraacetate, organic peracids such as peracetic acid and perbenzoic acid, inorganic peracids or salts thereof such as potassium permanganate, sodium metaperiodate, sodium perchlorate, and persulfuric acid, alcohol hydroperoxide such as tertiary-butyl-hydroperoxide and cumene hydroperoxide, halogen, selenium dioxide, ruthenium tetroxide, iodosobenzene, N-bromosuccinimide, dinitrogen pentoxide, etc.

Though the presence of a solvent is not essential, particularly in the case where a liquid oxidizing agent is employed, the reaction of this invention is usually carried out in a suitable solvent, for the purpose of accelerating the reaction or of avoiding side-reactions. The solvent is exemplified as water, alcohols (e.g. methanol, ethanol), organic acids (e.g. acetic acid, butyric acid, formic acid), halogenated hydrocarbons (e.g. chloroform, carbon tetrachloride, ethylene chloride), hydrocarbons (e.g. benzene, toluene, hexane), ethers (e.g. tetrahydrofuran, dioxane), ketones (e.g. acetone, methylethylketone), or the like.

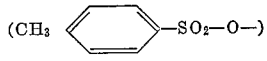
The reaction may proceed under alkaline, neutral or acid conditions in said solvent, preferably pH varying with the objective compound or oxidizing agent employed, for example, when hydrogen peroxide or peracids are employed as the oxidizing agents, weakly alkaline conditions are desirable for preparing sulfoxide derivatives, and weakly acid conditions are desirable for preparing sulfone derivatives.

The reaction temperature is suitably selected depending on the objective compounds and the oxidizing agents employed; that is, for preparing sulfoxide derivatives, the reaction is usually carried out employing, for example, sodium metaperiodate, cumene hydroperoxide, N-bromosuccinimide, etc., at room temperature (about 20° to about 30° C.) or under cooling. Alternatively, the sulfoxide derivatives are also obtained by a reaction employing less than an equivalent amount of a drastic oxidizing agent such as hydrogen peroxide, potassium permanganate, etc. under cooling, or, if desired, at room temperature, or at a temperature lower than 60° C., desirably lower than 40° C. On the other hand, for preparing sulfone derivatives, the reaction is usually carried out at room temperature or under heating; however, the reaction may also be carried out under cooling. In brief, the sulfoxide derivatives can be prepared by employing a mild oxidizing agent or by employing a drastic oxidizing agent under mild conditions, while the sulfone derivatives can be prepared by employing more than two equivalents of an oxidizing agent and under more drastic conditions than those employed for preparing the sulfoxide derivatives. A mixture of sulfoxides and sulfones is sometimes obtained depending upon the reaction conditions, and the mixture is useful as it is for an anti-inflammatory agent, etc.; therefore it is not always necessary to separate the mixture into each component.

Among the present compounds, the 2,4- or 2,6-dihalobenzyl methyl sulfones (I) can also be prepared by allowing the compound of the formula



to react with the compound of the formula CH_3Y_2 wherein X has the same significance as above, and one of the Y_1 and Y_2 is halogen (e.g. Cl, Br, etc.) or tosyloxy



and the other is the $-SO_2$-alkali metal (e.g. $-SO_2$-sodium, $-SO_2$-potassium, $-SO_2$-ammonium, etc.) radical. In the reaction the halogen attached to the aromatic ring does not react with the compounds having an $-SO_2$-alkali metal radical. The present reaction is usually carried out in a suitable solvent such as water, alcohol (e.g. methanol, ethanol), aromatic hydrocarbon (e.g. benzene, toluene, xylene), ether (e.g. dioxane), or the like, or a mixture thereof. The reaction is accelerated by heating, and completed usually in 3 to 10 hours.

The sulfoxides and sulfones (I) are useful as anti-inflammatory agents and are generally administered in the form of capsule, syrup, oil, injection, ointment, tablet, etc., i.e. orally, parenterally or topically. Pharmaceutical compositions containing one or more of the dialkyl-sulfoxides or sulfones (I) can be prepared according to any per se conventional means for the preparation of capsules, syrups, oils, injections, etc.

In the various aforesaid administrational forms, the active ingredient (I) may be present in a minor proportion with the carrier constituting the major proportion. However, the reverse relationship may also exist, so that a minor proportion of carrier is employed in association with a major proportion of active ingredient. Examples of administrational compositions are hereinafter exemplified.

The compounds (I) are also helpful in relieving disorders such as edema, and in alleviating pain and fever in acute or chronic rheumatoid arthritis and other musculoskeletal disorders.

A typical effective daily dose of the sulfoxides and sulfones (I) for an adult is usually about 100 mg. to 3 g. desirably 0.5 to 1 g., although an increased or reduced daily dose is also effective depending on the severity of the inflammation being treated, the indicated dose being especially suitable against inflammation caused e.g. by rheumatic fever.

It is to be understood that the following examples are solely for the purpose of illustration and not to be construed as limitations of this invention, and that minor variations may be resorted to without departing from the spirit and scope of this invention. In the said examples, "g.," "ml.," and "mg." stand for "gram(s)," "milliliter(s)" and "milligram(s)," respectively. Temperatures are all uncorrected, and percentages are all on the weight basis.

EXAMPLE 1

To 6.2 g. of 2,6-dichlorobenzyl methyl sulfide dissolved in 20 ml. of acetic acid, there is stirred in dropwise in 10 minutes 3.6 g. of a 30% aqueous solution of hydrogen peroxide dissolved in 20 ml. of acetic acid, then the mixture solution is stirred for further 10 minutes, followed by further stirring for one hour at room temperature. To the solution is added a saturated aqueous solution of sodium sulfite to decompose excess hydrogen peroxide and then the resultant solution is subjected to evaporation under reduced pressure to remove the solvent. To the oily residue, there is added water, and the mixture is agitated to precipitate crystals. The crystals are washed with water, and then recrystallized from carbon tetrachloride to obtain 6.3 g. of 2,6-dichlorobenzyl methyl sulfoxide as needles melting at 116–118° C. Yield: 94%.

EXAMPLE 2

To a solution of 3.1 g. of 2,6-dichlorobenzyl methyl sulfide in 20 ml. of acetic acid, there is added under stirring 318 g. of 30% aqueous hydrogen peroxide, and the mixture solution is stirred for 4 hours at 70–80° C. After cooling, there is added to the resultant solution a saturated aqueous solution of sodium sulfite to decompose excess hydrogen peroxide and subjected to evaporation under reduced pressure to remove the solvent. To the oily residue, there are added water and chloroform, and the cholorform layer is separated. The chloroform layer, after being washed with water and dried, is subjected to evaporation under reduced pressure to leave solid residue, which is recrystallized from ethanol to give 3.3 g. of 2,6-dichlorobenzyl methyl sulfone as flakes melting at 102–103° C. Yield: 92%.

EXAMPLE 3

To 4 g. of 2,4-dichlorobenzyl methyl sulfide dissolved in 20 ml. of acetic acid, there is added dropwise in 30 minutes under stirring 2 g. of 30% aqueous solution of hydrogen peroxide dissolved in 10 ml. of acetic acid under ice-cooling and then the mixture solution is further stirred for one hour at room temperature. To the reaction solution, there is added a saturated aqueous solution of sodium sulfite to decompose excess hydrogen peroxide and then the resultant solution is subjected to evaporation under reduced pressure to remove the solvent. To the desidue, there is added chloroform and water, and the mixture is shaken thoroughly, followed by separation of chloroform layer. The chloroform layer, after being washed with water and dried, is subjected to evaporation under reduced pressure to remove the solvent, and the oily residue is recrystallized from ether to give 4 g. of 2,4-dichlorobenzyl methyl sulfoxide as flakes melting at 59° C. Yield: 93%.

EXAMPLE 4

To a solution of 4 g. of 2,4-dichlorobenzyl methyl sulfide dissolved in 20 ml. of acetic acid, there is added under stirring 6 g. of 30% aqueous solution of hydrogen peroxide and the mixture solution is stirred for 4 hours at 70–80° C. After cooling, there is added to the resultant solution a saturated aqueous solution of sodium sulfite to decompose excess hydrogen peroxide, and then subjected to evaporation to remove the solvent. To the residue, there is added chloroform and water and the resultant mixture is shaken thoroughly, followed by separation of the chloroform layer. The chloroform layer, after being washed with water and dried, is subjected to evaporation to remove the solvent, and the resultant residue is recrystallized from ethanol to give 4.3 g. of 2,4-dichlorobenzyl methyl sulfone as needles melting at 112° C. Yield: 93%.

EXAMPLE 5

To 2.2 g. of 2-bromo-6-chlorobenzyl methyl sulfide dissolved in 15 ml. of acetic acid, there is added dropwise under stirring 1.1 g. of 30% aqueous solution of hydrogen peroxide dissolved in 10 ml. of acetic acid, and then the mixture solution is further stirred for one hour at room temperature. To the reaction solution, there is added a saturated aqueous solution of sodium sulfite to decompose excess hydrogen peroxide and then the resultant solution is subjected to evaporation under reduced pressure to remove the solvent. To the oily residue, there is added water and the mixture is agitated to precipitate crystals. The crystals, after being washed with water, are recrystallized from carbon tetrachloride to give 2.3 g. of 2-bromo-6-chlorobenzyl methyl sulfoxide as prisms melting at 122–124° C. Yield: 97%.

EXAMPLE 6

To a solution of 2.2 g. of 2-bromo-6-chlorobenzyl methyl sulfide in 30 ml. of acetic acid, there is added dropwise 2.4 g. of 30% aqueous hydrogen peroxide and the mixture is stirred for 4 hours at 70–80° C. After cool-

ing the reaction solution a saturated aqueous solution of sodium sulfite is added thereto to decompose excess hydrogen peroxide and then the resultant solution is subjected to evaporation under reduced pressure to remove the solvent. To the oily residue, there is added chloroform and water, and the mixture is shaken thoroughly, followed by separation of the chloroform layer. The chloroform layer, after being washed with water and dried, is subjected to evaporation to remove the solvent, and to the oily residue there is added petroleum ether to precipitate the crystals. The crystals are recrystallized from carbon tetrachloride to give 2 g. of 2-bromo-6-chlorobenzyl methyl sulfone as needles melting at 121–123° C. Yield: 80%.

EXAMPLE 7

To 2.0 g. of 2-chloro-6-fluorobenzyl methyl sulfide dissolved in 30 ml. of acetic acid, there is added dropwise under stirring 3 g. of 30% aqueous solution of hydrogen peroxide and then the mixture is further stirred for 4 hours at 70–80° C. After cooling the reaction solution a saturated aqueous solution of sodium sulfite is added thereto to decompose excess hydrogen peroxide and the resultant solution is subjected to evaporation to remove the solvent. To the residue, there are added chloroform and water and the mixture is shaken thoroughly, followed by separation of the chloroform layer. The chloroform layer, after being washed with water and dried, is subjected to evaporation under reduced pressure to remove chloroform and the residue is recrystallized from carbon tetrachloride to give 1.9 g. of 2-chloro-6-fluorobenzyl methyl sulfone melt-in gat 79–81° C. Yield: 81%.

EXAMPLE 8

To 3.8 g. of 2-chloro-6-fluorobenzyl methyl sulfide dissolved in 30 ml. of acetic acid, there is added dropwise under stirring 2 g. of 30% aqueous solution of hydrogen peroxide dissolved in 10 ml. of acetic acid and then the mixture solution is further stirred for one hour at room temperature. The resultant solution is subjected to evaporation under reduced pressure to remove the solvent. The residue is dissolved in chloroform and the resultant solution is washed with an aqueous solution of sodium hydrogencarbonate and then with a saturated aqueous solution of sodium sulfite. After drying, the solution is subjected to evaporation to remove chloroform, and to the resultant residue, there is added petroleum ether to yield crystals. The crystals are recrystallized from ligroin to give 3.4 g. of 2-chloro-6-fluorobenzyl methyl sulfoxide as flakes melting at 89–91° C. Yield: 83%.

EXAMPLE 9

A mixture of 12 g. of 2,6-dichlorobenzyl bromide, 6 g. of finely-powdered sodium methanesulfinate and 100 ml. of 80% ethanol is refluxed for 8 hours. After an irritative odor is distinguished, the resultant solution is concentrated to dryness under reduced pressure. To the residue, there is added water to dissolve produced sodium bromide and sodium methanesulfinate, and water insolubles are filtered off from the resultant solution. The substance is recrystallized from ethanol to give 10.7 g. of 2,6-dichlorobenzyl methyl sulfone as plates melting at 102–103° C. Yield: 89%.

EXAMPLE 10

A mixture of 9.7 g. of 2,4-dichlorobenzyl chloride, 6 g. of finely-powdered sodium methanesulfinate and 100 ml. of methanol is refluxed for 10 hours and the resultant solution is subjected to distillation under reduced pressure to remove methanol. To the residue, there is added water and the resultant mixture is filtered to obtain a water-insoluble solid substance. The solid substance is recrystallized from ethanol to give 10.2 g. of 2,4-dichlorobenzyl methyl sulfone as crystals melting at 112° C. Yield: 85%.

EXAMPLE 11

9.7 g. of 2,6-dichlorobenzyl chloride and 4.9 g. of ammonium methanesulfinate are reacted in the same manner as in Example 10, to give 10.2 g. of 2,6-dichlorobenzyl methyl sulfone. Wield: 85%.

EXAMPLE 12

A mixture of 2.8 g. of 2-chloro-6-bromobenzyl bromide, 1.1 g. of sodium methanesulfinate and 50 ml. of methanol is refluxed for 3 hours. The reaction mixture is subjected to distillation under reduced pressure to remove methanol and the residue is mixed thoroughly with water, followed by filtration. After drying, the water-insoluble solid is recrystallized from carbon tetrachloride to give 2.4 g. of 2-chloro-6-bromobenzyl methyl sulfone melting at 121–123° C. Yield: 75%.

EXAMPLE 13

A mixture of 5.6 g. of 2-chloro-6-fluorobenzyl bromide 27 g. of sodium methanesulfinate and 50 ml. of methanol is refluxed for hours. The resultant solution is subjected to distillation under reduced pressure to remove methanol. The residue is mixed with a small quantity of water and from the mixture, water-insoluble crystals are separated. After washing with water and drying, the crystals are recrystallized from carbon tetrachloride to give 5 g. of 2-chloro-6-fluorobenzyl methyl sulfone melting at 79–81° C. Yield: 90%.

EXAMPLE 14

2,6-dichlorobenzyl methyl sulfide (4.1 g.) is added little by little with stirring to a solution of sodium metaperiodide (4.3 g.) in 80 ml. of water while keeping the reaction temperature not higher than 5° C. with ice. After agitating for one hour, the reaction solution is saturated with sodium chloride. So-saturated solution is shaken with 200 ml. of chloroform. The chloroform layer is separated and then dried, followed by concentration under reduced pressure to leave oily residue, from which 3.2 g. of 2,6-dichlorobenzyl methyl sulfoxide is obtained by recrystallization from carbon tetrachloride, as needless melting at 116–118° C.

EXAMPLE 15

A chloroform solution (30 ml.) containing 0.0535 g. of perbenzoic acid per ml. is added gradually to a solution of 2.0 g. of 2,4-dichlorobenzyl methyl sulfide in 30 ml. of chloroform with stirring, under cooling with ice to keep the reaction temperature lower than 5° C.

The reaction solution is agitated for one hour, then 10 ml. of 0.1 normal aqueous sodium thiosulfate is added thereto, followed by vigorous stirring. The chloroform layer is washed with 10% aqueous potassium carbonate solution and then with a saturated aqueous solution of sodium chloride, followed by drying. The solvent is then distilled off to leave 1.8 g. of 2,4-dichlorobenzyl methyl sulfoxide as an oily substance, which is recrystallized from ether to give flakes melting at 59° C.

EXAMPLE 16

6 ml. of a toluene solution containing 0.76 g. of cumene hydroperoxide per ml. is added to a solution of 1.9 g. of 2-chloro-6-fluorobenzyl methyl sulfide in 20 ml. of chloroform with stirring under cooling with ice. After agitating for one hour, the reaction solution is left for 3 days at room temperature.

After the solvent is distilled off under reduced pressure, the residue is shaken with a mixture of water and chloroform. The chloroform layer, after being washed with water and dried, is subjected to distillation to remove the solvent, and the residue is recrystallized from ligroin to give 1.5 g. of 2-chloro-6-fluorobenzyl methyl sulfoxide as flakes melting at 89–91° C.

As indicated hereinbefore, the new compounds of the present invention can be administered in a variety of

forms of composition, some examples of which are as follows:

Composition 1

	Milligrams per tablet
2,6-dichlorobenzyl methyl sulfoxide	100.0
Milk sugar	200.0
Starch	78.0
Starch paste (dried)	20.0
Magnesium stearate	2.0
	400.0

The compound and milk sugar were admixed and the admixture was granulated with 15% starch paste. The granules were dried, screened, lubricated and compressed into tablets. The tablets thus prepared may further be coated with a coating material such as sugar.

The 2,6-dichlorobenzyl methyl sulfoxide can be replaced by a corresponding quantity of 2,6-dichlorobenzyl methyl sulfone or of any other herein-disclosed compound I.

Composition 2

	Milligrams
2,6-dichlorobenzyl methyl sulfoxide	100
Lactose	700
Starch	200
	1000

All ingredients are thoroughly mixed, the resultant admixture being a composition useful as an "oral powder."

Composition 3

2,6-dichlorobenzyl methyl sulfoxide is intimately admixed with white petrolatum and the resultant ointment dispensed via a collapsible tube. The amount of petrolatum is such that a one-inch expressed amount of ointment contains 10 to 20 milligrams for topical application.

Composition 4

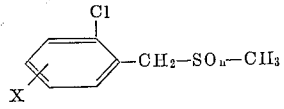
As hereinbefore indicated, the active ingredient may constitute a major proportion of the administered composition. Thus a composition may comprise, for example.

	Milligrams
2,6-dichlorobenzyl methyl sulfone	270
Lactose	25
Corn meal	100
Magnesium stearate	5
	400

This intermediate (concentrate) mixture is made up in per se conventional manner into unit dosage tablets.

Having thus disclosed the invention, what is claimed is:

1. A compound of the formula



wherein X is a member selected from the group consisting of Cl, Br and F attached to the 6-position, or Cl attached to the 4-position, and n is 1 or 2.

2. A compound as claimed in claim 1, wherein n is 2.

3. A compound as claimed in claim 2, namely, 2,6-dichlorobenzyl methyl sulfone.

4. A compound as claimed in claim 2, namely, 2,4-dichlorobenzyl methyl sulfone.

5. A compound as claimed in claim 2, namely, 2-chloro-6-fluorobenzyl methyl sulfone.

6. A compound as claimed in claim 2, namely, 2-chloro-6-bromobenzyl methyl sulfone.

7. A compound as claimed in claim 1, wherein n is 1.

8. A compound as claimed in claim 7, namely, 2,6-dichlorobenzyl methyl sulfoxide.

9. A compound as claimed in claim 7, namely, 2-chloro-6-bromobenzyl methyl sulfoxide.

10. A compound as claimed in claim 7, namely, 2-chloro-6-bromobenzyl methyl sulfoxide.

11. A compound as claimed in claim 7, namely, 2-chloro-6-fluorobenzyl methyl sulfoxide.

References Cited

Orda et al.: "Chem. Abstracts," vol. 63 (1965), pp. 1684–85.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,465,044 Dated September 2, 1969

Inventor(s) HIROSHI HIRANO, KATSUTADA MASUDA, KIYOHISA KAWAI and NOBORU SHIMAHARA

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

On column 1, line 9, before March 8, 1966, insert

February 28, 1966, 41/12443

Signed and sealed this 22nd day of February 1972.

(SEAL)
Attest:

EDWARD M.FLETCHER,JR.
Attesting Officer

ROBERT GOTTSCHALK
Commissioner of Patents