

PATENT SPECIFICATION

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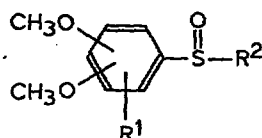


(54) ARYLALKYLSULPHOXIDES

(71) We, RECKITT & COLMAN PRODUCTS LIMITED, a British Company of Dansom Lane, Hull, Yorkshire, do hereby declare the invention for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to arylalkylsulphoxides and methods for their preparation.

According to this invention there are provided compounds of the formula



in which R¹ represents a hydrogen atom or a methoxy group, and R² represents an alkyl group having 1 to 7 carbon atoms, an alkenyl or alkynyl group having 3 to 5 carbon atoms, or a hydroxyalkyl group having 2 or 3 carbon atoms.

These compounds produce a significant reduction in blood pressure when administered to normotensive, DOCA or renal rats and also cats and dogs and have utility in the treatment of those conditions in man for which an anti-hypertensive or vasodilator drug is employed. By DOCA rats is meant rats rendered hypertensive by the administration of deoxycorticosterone acetate (DOCA) following unilateral nephrectomy.

Pharmaceutical compositions incorporating the compounds are described in the Specification of and claimed in co-pending Patent application No. 58065/70 (Serial No. 1,337,575).

The compounds may be prepared by oxidising the corresponding thioethers.

The oxidation may be carried out employ-

ing as the oxidising agent hydrogen peroxide, N-halosuccinimides, and 1 - chlorobenzotriazole. In order to minimise the formation of a further oxidation product, the sulphone, an equimolar proportion of the oxidising agent should be employed, and the oxidation conducted at 0—20°C.

Conveniently the thioether in glacial acetic acid is treated with an equimolar portion of hydrogen peroxide at 0—20°C.

The following examples illustrate the preparation of compounds of said formula:—

Example 1.

3,4 - Dimethoxyphenylmethyl sulphoxide
 3,4 - Dimethoxythiophenol (28.3g, 0.17 mole; A.A. Levi and S. Smiles. J. Chem. Soc. 520 (1931)) was added to sodium (3.83g., 0.17 mole) in absolute ethanol. Dimethyl sulphate (20.8g., 0.17 mole) was slowly added to the mixture which was then refluxed for two hours. The solvent was removed under reduced pressure. The residue was extracted with chloroform. The extracts were washed with water, dried over magnesium sulphate and evaporated to give 3,4 - dimethoxyphenylmethyl sulphide (28.6g) b.p. 110°C/0.8mm.

Anal. Calcd. for C₉H₁₂O₂S:

C,58.7: H,6.6: S,17.4

Found:

C,58.5: H,6.4: S,17.2%

30% Hydrogen peroxide (11.3ml., 0.1 mole) was added to the 3,4 - dimethoxyphenylmethyl sulphide (18.4g, 0.1 mole) in glacial acetic acid (100ml) with cooling. The mixture after remaining at room temperature for 24 hours was made alkaline by the slow addition of ice-cold aqueous sodium hydroxide. The mixture was extracted with chloroform. The extracts were

- washed with water, dried over magnesium sulphate and evaporated to dryness under reduced pressure to give white crystalline 3,4-dimethoxyphenylmethyl sulphoxide (15.1g).
- 5 A sample recrystallised from diisopropyl ether had m.p. 82—84°C.

Anal. Calcd. for $C_9H_{12}O_3S$:
C,54.1: H,6.1: S,16.0

Found:

- 10 C,53.9: H,6.3: S,15.7%

Example 2.

3,4 - Dimethoxyphenylethyl sulphoxide

- 3,4 - Dimethoxythiophenol (8.6g., 0.05 mole), sodium (1.15g., 0.05 mole), ethanol (50ml) and ethyl iodide (7.8g., 0.05 mole) were reacted according to the manner of Example 1 to give 3,4 - dimethoxyphenylethyl sulphide (7.3g) b.p. 100—108°C/0.2mm.
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Anal. $C_{10}H_{14}O_2S$ requires:

- 20 C,60.7: H,7.1: S,16.2

Found:

C,60.7: H,7.0: S,15.9%

- The 3,4 - dimethoxyphenylethyl sulphide (1.98g) was oxidised, according to the manner of Example 1, to give 3,4 - dimethoxyphenylethyl sulphoxide (1.6g).
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Anal. Calcd. for $C_{10}H_{14}O_3S$:

C,56.1: H,6.6

Found:

- 30 C,56.0: H,6.4%

Example 3.

2,5 - Dimethoxyphenylmethyl sulphoxide

- 2,5 - Dimethoxythiophenol (2.8g., 0.017 mole; Suter and Hansen J. Am. Chem. Soc 54, 4102, (1932)) was added to sodium (0.4g., 0.017 mole) in absolute ethanol. Dimethyl sulphate (2.1g., 0.017 mole) was slowly added to the mixture which was then refluxed for two hours. The solvent was removed under reduced pressure. The residue was extracted
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with chloroform. The extracts were washed with water, dried over magnesium sulphate and evaporated to give 2,5 - dimethoxyphenylmethyl sulphide (2.8g) b.p. 92—96°C/0.3mm.

Anal. Calcd. for $C_9H_{12}O_2S$:

C,58.7: H,6.6: S,17.4

Found:

C,59.0: H,6.5: S,17.5%

The 2,5 - dimethoxyphenylmethyl sulphide (2.3g) was oxidised according to the manner of Example 1 to give 2,5 - dimethoxyphenylmethylsulphoxide (1.8g) m.p. 70—72°C.

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Anal. Calcd. for $C_9H_{12}O_3S$:

C,54.1: H,6.1: S,16.0

Found:

C,53.5: H,6.0: S,16.5%

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The table sets out details of further examples of compounds prepared by the oxidation of the corresponding thioethers by the method of Example I.

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For the purposes of treatment of patients the compounds are administered as pharmaceutical compositions. The pharmaceutical compositions may be in a form suitable for oral administration or in a form suitable for parenteral administration. Compositions intended for oral use may be in the form of tablets, packaged powder or granules, aqueous or oily suspensions, emulsions, hard or soft capsules, lozenges or syrups.

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Compositions intended for parenteral administration may be in the form of sterile injectable preparations such as solutions or suspensions in water, saline or 1,3 - butane diol. The preparations may also contain suitable wetting agents and suspending agents.

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For the purposes of convenience and accuracy of dosing the compositions are advantageously employed in a unit dosage form. For oral administration the unit dosage form contains from 1mg to 500mg, preferably from 10mg to 100mg, of the compound of said formula. Parenteral unit dosage forms contain from 1mg to 10mg of the compound of said formula per 1ml of the preparation.

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Table

Ex- ample	Substituent on Benzene Ring					R ²	m.p. °C	Formula	% Calcd.			% Found		
	2	3	4	5	6				C	H	S	C	H	S
4		MeO	MeO			n-Pr	-	C ₁₁ H ₁₆ O ₃ S	57.9	7.1	14.1	57.7	7.0	13.6
5		MeO	MeO			i-Pr	68-70	C ₁₁ H ₁₆ O ₃ S	57.9	7.1	14.1	57.9	6.9	14.1
6		MeO	MeO			n-Bu	-	C ₁₂ H ₁₈ O ₃ S	59.5	7.5		59.5	7.6	
7		MeO	MeO			i-Bu	-	C ₁₂ H ₁₈ O ₃ S	59.5	7.5		58.9	7.4	
8		MeO	MeO			CH ₂ CH=CH ₂	-	C ₁₁ H ₁₄ O ₃ S	58.5	6.2		58.5	6.3	
9		MeO	MeO			CH ₂ CH ₂ OH	125-6	C ₁₀ H ₁₄ O ₄ S	52.2	6.1	13.9	51.8	6.1	13.8
10	MeO		MeO			Me	-	C ₉ H ₁₂ O ₃ S	54.1	6.1		53.7	6.0	
11	MeO			MeO		n-Pr	-	C ₁₁ H ₁₆ O ₃ S	57.9	7.1		57.9	7.3	
12	MeO			MeO		i-Pr	-	C ₁₁ H ₁₆ O ₃ S	57.9	7.1		57.7	6.9	
13	MeO			MeO		n-Bu	-	C ₁₂ H ₁₈ O ₃ S	59.5	7.5	13.3	59.3	7.2	12.8
14	MeO			MeO		i-Bu	-	C ₁₂ H ₁₈ O ₃ S	59.5	7.5		59.3	7.2	
15	MeO			MeO		CH ₂ CH=CH ₂	-	C ₁₁ H ₁₄ O ₃ S	58.5	6.2		58.8	6.3	
16	MeO			MeO		CH ₂ CH ₂ OH	108-110	C ₁₀ H ₁₄ O ₄ S	52.2	6.1	13.9	52.4	6.1	14.1

Table cont'd

Ex- ample	Substituent on Benzene Ring						R ²	m.p. °C	Formula	% Calcd.			% Found		
	2	3	4	5	6					C	H	S	C	H	S
17		MeO	MeO	MeO			Me	74-6	C ₁₀ H ₁₄ O ₄ S	52.2	6.1	13.9	52.2	6.1	13.9
18		EtO	EtO				Me	61-2	C ₁₁ H ₁₆ O ₄ S	57.9	7.1	14.1	57.6	6.9	14.0
19	MeO	MeO					Me	-	C ₉ H ₁₂ O ₃ S	54.1	6.1	16.0	54.1	6.0	16.2
20	MeO				MeO		Me	97-8	C ₉ H ₁₂ O ₃ S	54.1	6.1	16.0	53.6	6.2	16.0
21		MeO		MeO			Me	74-6	C ₉ H ₁₂ O ₃ S	54.1	6.1	16.0	54.3	6.2	15.7
22		EtO	EtO			n-Pr	n-Pr	-	C ₁₃ H ₂₀ O ₃ S	61.0	7.9	12.5	60.7	8.2	12.0
23		MeO	MeO	MeO		n-Am	n-Am	-	C ₁₃ H ₂₀ O ₃ S	61.0	7.9	12.5	60.6	8.0	12.0
24		MeO	MeO	MeO		n-C ₄ H ₉	n-C ₄ H ₉	-	C ₁₅ H ₂₄ O ₃ S	63.4	8.5	11.3	63.4	8.5	11.4
25		MeO	MeO	MeO	Me	Me	Me	92-3	C ₁₀ H ₁₄ O ₃ S	56.1	6.6	15.0	56.0	6.5	14.9
26		MeO	MeO	MeO	MeO	Me	Me	117-9	C ₁₀ H ₁₄ O ₄ S	52.2	6.1	13.9	52.7	6.2	12.5

The following pharmaceutical preparations are also described:—

Preparation I

- 5 A mixture of 1 part of 3,4 - dimethoxyphenylmethyl sulphoxide, 5 parts of lactose and 5 parts of starch, together with 1% of magnesium stearate was compressed into tablets. Conveniently the tablets are of such a size as to contain 10 or 25 mg of 3,4 - dimethoxyphenylmethyl sulphoxide. Similarly
10 tablets containing 50mg of 3,4 - dimethoxyphenylmethyl sulphoxide were prepared from a mixture of 2 parts of the sulphoxide, 5 parts of lactose, 5 parts of starch together with 1%
15 magnesium stearate.

Preparation II

A mixture of 1 part of 3,4 - dimethoxyphenylmethyl sulphoxide, and 9 parts of a tablet base comprising starch with the addition of 1% magnesium stearate was compressed
20 into tablets.

Conveniently the tablets are of such a size as to contain 10 or 25mg of 3,4-dimethoxyphenylmethyl sulphoxide. Similarly tablets containing 50mg of 3,4-dimethoxyphenylmethyl sulphoxide were prepared from a mixture of 2 parts of the sulphoxide, 9 parts of starch together with 1% magnesium stearate.
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Preparation III

Various strength capsules are prepared containing 3,4 - dimethoxyphenylmethyl sulphoxide and the following ingredients (amounts are in mg):—
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	Sulphoxide	Magnesium stearate	Calcium phosphate	Lactose
35	10	2	—	190
	25	2	—	175
	50	3	—	150
	100	3	—	100
40	10	—	20	170
	25	—	20	155
	50	—	20	130
	100	—	20	80

- 45 The above ingredients may be screened through a 40 B.S.S. mesh screen before being mixed and filled into hard gelatine capsules.

Preparation IV

- 50 Ampoules were prepared containing 5 mls of an isotonic solution prepared from 1 gm 3,4-dimethoxyphenylmethyl sulphoxide and 0.735 gm sodium chloride in 100 mls distilled water. The solution was stable to steam autoclaving at 10 psi for 35 minutes.

Preparation V

- 55 The 3,4 - dimethoxyphenylmethyl sulphoxide in each of the foregoing preparations I—IV may be replaced by 2,4 - dimethoxyphenylmethyl sulphoxide, 3,4 - dimethoxyphenylethyl sulphoxide, 2,5 - dimethoxyphenylmethyl sulphoxide, 3,4 - dimethoxyphenylpropyl sulphoxide, 3,4,6 - trimethoxyphenylmethyl sulphoxide, or 3,5 - dimethoxyphenylmethyl sulphoxide.
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- 65 Screening for antihypertensive activity has been carried out employing known pharma-

cological tests such as those using normotensive, DOCA and renal hypertensive rats according to the method of Stanton H.C. and White J.B., Archs. Int. Pharmacodyn. Ther. 154, No. 2, 351 (1966) and Weeks J.R. and Jones J.A., Proc. Exper. Biol. & Med. 104, No. 4, 646 (1960).
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The following are some of the test results obtained with compounds of said formula. The compounds were administered intraperitoneally at a dose of 100mg/kg to groups of DOCA hypertensive rats, and the figures are for the maximum percentage fall in the blood pressure
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Compound of Example No.	% Fall in Blood Pressure	
1	65	80
2	50	
3	46	
4	30	85
21	50	
26	51	

The following are some of the results when compounds were administered orally to groups of DOCA hypertensive rats at dosage levels

of 20, 50 and 100 mg/kg. At each dose level a group of 6 rats was employed for each compound. The figures are for the maximum percentage fall in the blood pressure.

	Compound of Example No.	% Fall in Blood Pressure		
		20	50	100 mg/kg dose
10	1	30	36	53
	2	21	34	50
	3	5	14	21
	4	16	28	42
15	10	18	18	26
	18	24	28	44

It is expected that the likely human oral dose of a composition will be 200—500 mg of active ingredient per day for the relief of hypertension.

It has been shown that these compounds possess interesting and prolonged vasodilator actions which are exerted on the smooth muscle fibres of the blood vessels of the peripheral circulation. There is no action on the autonomic nervous system. That the vasodilator activity is of peripheral origin is demonstrated by the following findings:—

1. The compounds have hypotensive activity in spinalised cats and pithed rats.

2. The compounds are active against vasoconstriction produced by noradrenaline and vasopressin in a variety of isolated perfused blood vessel preparation e.g. rabbit ear, rat mesenteric vessels.

Further the compounds antagonise the pressor effects of noradrenaline, tyramine and angiotensin in the anaesthetised cat and dog at 3 to 10 mg/kg. Nictitating membrane contractions were also antagonised.

in which R¹ represents a hydrogen atom or a methoxy group, and R² represents an alkyl group having 1 to 7 carbon atoms, an alkenyl or alkynyl group having 3 to 5 carbon atoms, or a hydroxyalkyl group having 2 or 3 carbon atoms.

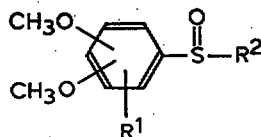
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3. 3,4 - Dimethoxyphenylpropyl sulphoxide.
4. 3,4 - Dimethoxyphenylethyl sulphoxide.
5. 2,5 - Dimethoxyphenylmethyl sulphoxide.
6. 3,5 - Dimethoxyphenylmethyl sulphoxide.
7. 3,4 - Diethoxyphenylmethyl sulphoxide.
8. 3,4 - Diethoxyphenylpropyl sulphoxide.
9. 3,4,6 - Trimethoxyphenylmethyl sulphoxide.

10. 3,4 - Dimethoxy - 6 - methylphenylmethyl sulphoxide.

11. Compounds of the formula of Claim 1 as hereinbefore described with reference to any one of the Examples 5 to 9, 11 to 17, 19 to 21, 23 and 24.

WHAT WE CLAIM IS:—

1. Compounds of the formula:—



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Compound of Example No.	% Fall in Blood Pressure		
	20	50	100 mg/kg dose
10	1	30	53
	2	21	34
	3	5	14
	4	16	28
15	10	18	18
	18	24	28
			44

It is expected that the likely human oral dose of a composition will be 200—500 mg of active ingredient per day for the relief of hypertension.

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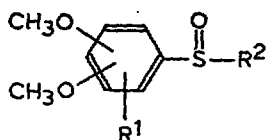
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5. 2,5 - Dimethoxyphenylmethyl sulphoxide.
6. 3,5 - Dimethoxyphenylmethyl sulphoxide.
7. 3,4 - Diethoxyphenylmethyl sulphoxide.
8. 3,4 - Diethoxyphenylpropyl sulphoxide.
9. 3,4,6 - Trimethoxyphenylmethyl sulphoxide.

10. 3,4 - Dimethoxy - 6 - methylphenylmethyl sulphoxide.

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