

1364 407

PATENT SPECIFICATION

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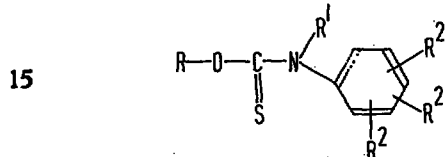


(54) THIOCARBAMIC ACID DERIVATIVES

(71) We, CARLO ERBA SPA, an Italian Body Corporate, of Via Carlo Imbonati 24, 20159 Milan, Italy, 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:—

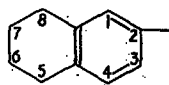
This invention relates to compounds which are thiocarbamic acid derivatives having antifungal activity, to a process for their preparation and to pharmaceutical compositions containing these derivatives.

The compounds of the invention have the general formula (I)

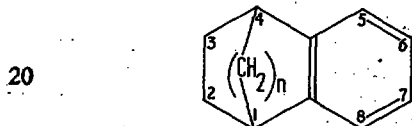


I

wherein R is a 5,6,7,8-tetrahydro-2-naphthyl group, i.e. a group of general formula



or R is a group of general formula



wherein n is 1, 2 or 3, R^1 is a hydrogen atom or a C_{1-6} alkyl group; and each of the groups R^2 , which may be the same or

different, is a hydrogen or halogen atom, a nitro, cyano, trihalomethyl, phenyl, C_{1-6} alkyl or C_{1-6} alkoxy group or a group of formula $-SR^3$, $-COR^3$ or $-NHCOR^3$ wherein R^3 is a C_{1-6} alkyl group.

The preferred compounds are those in which R^1 is an alkyl group and one of the R^2 groups is an alkyl or alkoxy group or a halogen atom, while the other two R^2 groups are hydrogen atoms. The alkyl groups may be branched or straight chain alkyl groups. The preferred alkyl group is the methyl group.

Examples of particularly preferred compounds are:

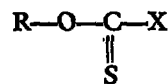
O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - tolyl)-thiocarbamate,

O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - tolyl)-thiocarbamate, and

O - (5,6,7,8 - tetrahydro - 2 naphthyl) - N-methyl - N - (m - tolyl) - thiocarbamate.

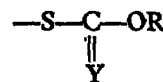
The compounds of general formula (I) may be prepared by

(a) reacting a compound of general formula (II)



II 50

wherein R is as defined above, and X is a halogen atom, a group of formula $-S-R^4$ wherein R^4 is an alkyl or substituted or unsubstituted phenyl group, or a group of formula

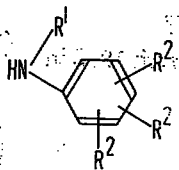


55

wherein R is as defined above and Y is an oxygen or sulphur atom, with an amine of general formula (III)

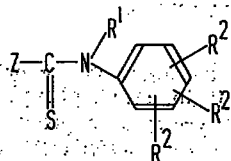
Price 75p

[Price 25p]



III

wherein R^1 and R^2 are as defined above; or
(b) reacting a compound of general formula (IV)



IV

wherein R^1 and R^2 are as defined above and Z is a halogen atom, with a compound of general formula (V)



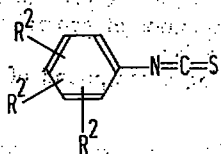
V

10 wherein R is as defined above and M is a hydrogen or metal atom; or
(c) reacting a compound of general formula (VI)



VI

15 wherein R is as defined above, with a compound of general formula (VII)



VII

20 wherein R^2 is as defined above, to give a compound of general formula (I) wherein R^1 is a hydrogen atom.

When X is a halogen atom in the compounds of general formula (II), it is preferably a chlorine atom. These compounds of general formula (II) may be prepared for example by reaction of the compounds of general formula (VIII)



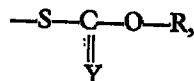
VIII

30 wherein W is preferably an alkali or alkaline earth metal atom, with thiophosgene, preferably performing the reaction in an organic solvent, for example chloroform or dioxan, and at 0° to 40° C, preferably 20–30° C. The compounds of general formula (VIII) may be prepared, in their turn, starting from the

compounds of general formula (VI) by known methods, for example by reaction with sodium hydroxide in a suitable solvent.

The compound of general formula (VI) wherein R is a 5,6,7-8-tetrahydro-2-naphthyl group is known in literature (see for example J. Am. Chem. Soc., 1947, 69, 578). The compound of general formula (VI) wherein R is the 1,4-methano-1,2,3,4-tetrahydro-6-naphthyl radical may be prepared for example by the method of Tetrahedron Letters, 1970, 14, 1145 starting from the corresponding methoxy derivative, described in for example in Can. J. Chem., 45 (11) 1185. The compound of general formula (VI) wherein R is a 1,4-ethano-1,2,3,4-tetrahydro-6-naphthyl group may be prepared, for example, by following the same method, starting from the corresponding methoxy derivative described for example in J. Org. Chem., 1971, 36 (3), 425. The compound of general formula (VI) wherein R is a 1,4-propano-1,2,3,4-tetrahydro-6-naphthyl radical may be prepared in a similar way.

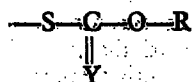
The compounds of general formula (II) wherein X is a $-S-R^4$ group are known in literature [see for example Bull. Soc. Chim. Fr. [3], 35, 838; Agr. Biol. Chem. 1969, 33(12), 1691]. The compounds of general formula (II) wherein X is



are also known (see for example J. Am. Chem. Soc. 1952, 74, 3647). The compounds of general formula (IV) are also known and may be obtained by means of methods known per se.

The reaction between the compounds of general formula (II), wherein X is halogen, and the compounds of general formula (III) is preferably performed in an organic solvent, for example chloroform or dioxan and in the presence of a hydrohalic acid acceptor, for example, sodium bicarbonate; however, the amine itself used in the reaction may act as the hydrohalic acid acceptor.

When the compounds of general formula (VIII) are reacted with thiophosgene, the compound of general formula (II) need not necessarily be isolated, it can be reacted direct with the compound of general formula (III) in the solution in the organic solvent, for example dioxan or chloroform, used in the reaction between the compounds of general formula (VIII) and thiophosgene. The reaction between the compounds of general formula (II), wherein X is a $-S-R^4$ group, with the compounds of general formula (III) is preferably performed in organic solvents, in particular aliphatic alcohols, at 20° to 60° C. The reaction between the compounds of general formula (II) wherein X is a



group, with the compounds of general formula (III) is preferably performed in organic solvents, preferably aliphatic alcohols e.g. ethanol, at -10° to $+20^{\circ}$ C.

The reaction between the compounds of general formula (IV) and the compounds of general formula (V) is preferably performed in organic solvents for example acetone, at 10° to 20° C.

The reaction between the compounds of general formula (VI) and the compounds of general formula (VII), which are known in the literature (see for example J. Chem. Soc., 125, 1704) may be performed for example at reflux temperature in an organic apolar solvent, for example benzene or toluene, preferably by adding to the reaction mixture a tertiary base, for example triethylamine.

The compounds of the present invention

possess a good topical antifungal activity of the fungicidal kind which is particularly efficacious against dermatophyte fungi, for example, *Trichophyton*, *Epidermophyton* and *Microsporum*, and are therefore useful in the treatment of the infections caused by these microorganisms.

Table I shows for example the antifungal activity of the compounds

O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - tolyl)-thiocarbamate (A)

O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - tolyl)-thiocarbamate (B), and

O - (5,6,7,8 - tetrahydro - 2 naphthyl) - N-methyl-N-(m-tolyl)-thiocarbamate (C)

in comparison with tolnaftate in guinea-pig skin infected by *Trichophyton asteroides* using the modified Weinstein's method (Antimicrobial Agents and Chemotherapy, 1964, 595-601). The results are shown in Table I.

TABLE I

Compound	Doses*	% Healed lesions	ED ₅₀	Potency ratio vs. tolnaftate
A	0.01	25.0		
	0.03	53.6	0.029	3.2
	0.10	77.9		
	1.00	100.0		
B	0.01	12.5		
	0.03	29.16	0.048	1.93
	0.10	70.83		
	1.00	100.0		
C	0.01	12.5		
	0.03	50.0	0.045	2.06
	0.10	62.5		
	1.00	100.0		
Tolnaftate	0.01	10.7		
	0.03	18.7	0.093	
	0.10	60.0		
	1.00	88.8		

* The doses are given as concentrations (p/v) of the solutions with which each treatment was performed.

In Table I the antifungal activity was assayed according to a microbiological control performed by means of agar-cultures of skin samples taken from the lesions and according to ED₅₀ values calculated following Litchfield and Wilcoxon's method (J. Pharmacol. Exp. Ther. 1949, 96, 99—113) on the basis of the percentage of the healed lesions, i.e.

negative to culture-control. As will be noted, the compounds of the invention have a surprisingly higher activity than tolinaftate.

Table II shows the activity ratio of Compound A and tolinaftate in guinea-pig skin infected with *Trichophyton asteroides*, when calculated according to a macroscopic evaluation of the lesions in "scores".

TABLE II

Doses*		0.01	0.03	0.10	1.00
Compound A	—				
	X (scores mean)	2.531	1.857	1.485	1.227
	n (lesions number)	32	28	68	44
	S.E. (standard error)	0.126	0.111	0.076	0.063
Tolnaftate	—				
	X	3.392	3.062	2.650	1.833
	n	28	32	60	36
	S.E.	0.187	0.190	0.171	0.129

Potency ratio vs. tolinaftate = 26.84.

* The doses are given as concentrations (p/v) of the solutions with which each treatment was performed.

The test of Table II was performed according to a factorial scheme with two products, i.e. Compound A and tolinaftate, each of them administered in four doses, following the parallel line biological assay method (Finney Statistical Method in Biological Assay, Griffin, London, 1952). The values obtained in three tests are given as an arithmetic mean and mean standard error.

The data reported in Table II show that the mean score relating to Compound A is lower than that of tolinaftate under all the doses tested, i.e. Compound A is more active. In order to give a quantitative evaluation of the difference between the two products, the activity ratio has been calculated by using the log dose-effect function reckoned on the basis of the data contained in the Table. Said ratio is 26.84 with variance limits (fiducial limits) ranging between 11.78 and 81.46 at a probability degree of 95%. The lower limit of 11.78 is much higher than 1 and this proves that there is a significant difference between the two products; this means that Compound A is always more active than tolinaftate.

Suitable forms for the administration of the compounds of the invention are for example solutions, ointments, creams as well as any other pharmaceutical composition indicated for the topical use. A suitable cream

for topical use contains 0.5 to 1 g of the compound per 100 g cream.

The invention therefore also provides a pharmaceutical composition comprising a compound of general formula (I) and a pharmaceutically acceptable carrier or diluent.

The following Examples illustrate the present invention.

EXAMPLE 1.

Thiophosgene (1.15 g; 0.01 mole) in chloroform (100 ml) was slowly treated with stirring with sodium 1,4-methano-1,2,3,4-tetrahydro-6-naphthoxide (1.82 g; 0.01 mole). After stirring for 30 minutes at ambient temperature, *m*-anisidine (2.46 g; 0.02 moles) in chloroform (50 ml) was added dropwise to the solution obtained. The mixture was then stirred for two hours at room temperature, the solvent evaporated, the residue redissolved in water and extracted with diethyl ether. The organic extracts gave, after drying (Na₂SO₄), evaporation, and crystallization from ethanol at 95° C, O-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-N-(*m*-methoxyphenyl)-thiocarbamate (1.2 g) m.p. 121—124° C.

By using the same method, the following compounds were obtained:

O-(1,4-methano-1,2,3,4-tetrahydro-6-

- naphthyl) - N - phenyl - thiocarbamate (after crystallisation from ethanol at 95°), m.p. 150—152° C;
- 3 O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (*m* - tolyl) - thiocarbamate (ethanol at 95°), m.p. 115—118° C;
- O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (*m* - chloro - phenyl) - thiocarbamate (ethanol at 95°), m.p. 119—122° C;
- 10 O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (*m* - nitro - phenyl) - thiocarbamate (cyclohexane), m.p. 129—131° C;
- O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (*p* - diphenyl) - thiocarbamate (isopropanol), m.p. 150—153° C;
- 15 O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (2 - methyl - 4 - chlorophenyl) - thiocarbamate (cyclohexane), m.p. 118—122° C;
- 20 O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (2 - methoxy - 5 - nitrophenyl) - thiocarbamate (absolute ethanol), m.p. 132—135° C;
- O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (*m* - trifluoromethyl - phenyl) - thiocarbamate (ethanol/water), m.p. 116—119° C;
- 25 O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (*m* - acetyl - phenyl) - thiocarbamate (absolute ethanol), m.p. 125—127° C;
- 30 O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (*m* - acetamido - phenyl) - thiocarbamate;
- 35 O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (*m* - cyano-phenyl) - thiocarbamate;
- O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (*m* - methylthio-phenyl) - thiocarbamate (cyclohexane), m.p. 103—104° C.
- carbamate (isopropyl alcohol), m.p. 94—97° C;
- O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (*p* - nitrophenyl) - thiocarbamate (ethyl acetate), m.p. 177—182° C;
- O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (*m* - chlorophenyl) - thiocarbamate (ethanol at 95°), m.p. 110—115° C;
- O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (*m* - nitrophenyl) - thiocarbamate (methanol), m.p. 123—126° C;
- O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (*m* - methoxyphenyl) - thiocarbamate (diisopropyl ether/petroleum ether), m.p. 82—84° C;
- O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (*p* - tolyl) - thiocarbamate (absolute ethanol), m.p. 98—101° C;
- O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (*p* - diphenyl) - thiocarbamate (petroleum ether), m.p. 104—107° C;
- O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - ethyl - N - phenyl - thiocarbamate (diisopropylether), m.p. 89—91° C;
- O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (*m* - trifluoromethylphenyl) - thiocarbamate (absolute ethanol), m.p. 113—116° C;
- O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (*m* - acetylphenyl) - thiocarbamate, (ligroin), m.p. 96—97° C;
- O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (*m* - acetamidophenyl) - thiocarbamate;
- O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (*m* - cyano-phenyl) - thiocarbamate;
- O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (*m* - methylthiophenyl) - thiocarbamate.

EXAMPLE 2.

- Thiophosgene (1.15 g; 0.01 mole) in chloroform (40 ml) was slowly treated at room temperature with sodium 1,4-methano-1,2,3,4-tetrahydro-6-naphthoxide (1.82 g; 0.01 mole). After 30 minutes, N-methyl-*m*-toluidine (2.42 g; 0.02 mole) in chloroform (40 ml) was added dropwise to the solution so obtained at room temperature. The reaction mixture was stirred for 48 hours at ambient temperature and then refluxed for two hours. The solvent was evaporated, and the residue redissolved in water and extracted repeatedly with diethyl ether. The organic phase was dried (Na₂SO₄) and evaporated to dryness to give, after crystallisation from isopropanol, O-(1,4-methano-1,2,3,4 - tetrahydro - 6 - naphthyl) - N-methyl - N - (*m* - tolyl) - thiocarbamate (1.3 g) m.p. 92—94° C.

By using the same method, the following compounds were obtained:

O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - phenyl - thio-

- EXAMPLE 3:
- Thiophosgene (0.575 g; 0.005 mole) in chloroform (40 ml) was slowly treated with stirring with sodium 1,4-ethano-1,2,3,4-tetrahydro-6-naphthoxide (0.98 g; 0.005 mole) at ambient temperature. After 30 minutes *m*-toluidine (1.01 g; 0.01 mole) in chloroform (30 ml) was added dropwise to the solution so obtained. The mixture was subsequently stirred for an hour at room temperature, the solvent was evaporated and the residue redissolved in water and extracted with diethyl ether. The organic phase, after drying (Na₂SO₄), evaporation to dryness and crystallisation from absolute ethanol gave O-(1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (*m* - tolyl)thiocarbamate (1.25 g.) m.p. 127—131° C.

By using the same method, the following compounds were obtained:

- O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - tolyl)-thiocarbamate (ethanol at 95°), m.p. 110—112° C;
- 5 O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - phenyl - thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (m - chloro - phenyl) - thiocarbamate;
- 10 O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (m - nitro - phenyl) - thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (p - diphenyl) - thiocarbamate;
- 15 O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (2 - methyl - 4 - chlorophenyl)-thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (2 - methoxy - 5 - nitrophenyl)-thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (m - trifluoromethyl - phenyl)-thiocarbamate;
- 20 O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (m - acetyl - phenyl) - thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (m - acetamido - phenyl)-thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (m - cyano-phenyl) - thiocarbamate;
- 25 O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (m - methylthio-phenyl)-thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - (m - methoxy - phenyl)-thiocarbamate;
- 30 O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - phenyl - thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - chlorophenyl)-thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - nitrophenyl)-thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (p - nitrophenyl)-thiocarbamate;
- 35 O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - methoxyphenyl)-thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - methoxyphenyl)-thiocarbamate;
- 40 O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - phenyl - thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - chlorophenyl)-thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - nitrophenyl)-thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (p - nitrophenyl)-thiocarbamate;
- 45 O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - chlorophenyl)-thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - nitrophenyl)-thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (p - nitrophenyl)-thiocarbamate;
- 50 O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - methoxyphenyl)-thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - methoxyphenyl)-thiocarbamate;
- 55 O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (p - tolyl)-thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (p - diphenyl)-thiocarbamate;
- 60 O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - ethyl - N - phenyl - thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - trifluoromethylphenyl)-thiocarbamate;
- 65 O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - acetylphenyl)-thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - acetamidophenyl)-thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - cyano-phenyl)-thiocarbamate;
O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6-naphthyl) - N - methyl - N - (m - methylthiophenyl)-thiocarbamate.

EXAMPLE 4.

Thiophosgene (5.75 g; 0.05 mole) in chloroform (100 ml) was treated slowly with sodium 5,6,7,8 - tetrahydro - 2 - naphthoxide (8.5 g; 0.05 mole) at ambient temperature. After stirring the suspension for about half an hour, N-methyl-m-toluidine (12.1 g; 0.1 mole) in chloroform (100 ml) was added at ambient temperature. After stirring for 12 hours at ambient temperature, the solvent was evaporated and the residue, dissolved in water, was extracted with diethyl ether. The ethereal extracts, after drying and evaporation, gave a crude oil which was purified by column chromatography and was then allowed to stand for a long time to obtain O-(5,6,7,8-tetrahydro - 2 - naphthyl) - N - methyl - N - (m-tolyl)-thiocarbamate (10.4 g) m.p. 48—51° C.

The following compounds were analogously prepared:

- O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N - (m-tolyl)-thiocarbamate (m.p. 108—112° C);
- O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N - phenyl-thiocarbamate;
- O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N - (m-chlorophenyl)-thiocarbamate;
- O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N - (m-nitrophenyl)-thiocarbamate;
- O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N - (p-diphenyl)-thiocarbamate;
- O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N - (2 - methyl - 4 - chlorophenyl) - thiocarbamate;
- O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N - (2 - methoxy - 5 - nitrophenyl) - thiocarbamate;
- O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N - (m-trifluoromethyl-phenyl)-thiocarbamate;
- O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N - (m-acetylphenyl)-thiocarbamate;
- O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N - (m-acetamidophenyl)-thiocarbamate;
- O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N - (m-cyanophenyl)-thiocarbamate;
- O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N - (m-methylthiophenyl)-thiocarbamate;
- O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N - (m-methoxyphenyl)-thiocarbamate;
- O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N - methyl-N-phenyl-thiocarbamate;
- O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N -

- methyl - N - (*m* - chlorophenyl) - thiocarbamate;
 O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N-methyl - N - (*m* - nitrophenyl) - thiocarbamate;
 O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N-methyl - N - (*p* - nitrophenyl) - carbamate;
 O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N-methyl - N - (*m* - methoxyphenyl) - thiocarbamate;
 O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N-methyl - N - (*p* - tolyl) - thiocarbamate;
 O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N-methyl - N - (*p* - diphenyl) - thiocarbamate;
 O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N-ethyl - N - phenyl - thiocarbamate;
 O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N-methyl - N - (*m* - trifluoromethylphenyl) - thiocarbamate;
 O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N-methyl - N - (*m* - acetylphenyl) - thiocarbamate;
 O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N-methyl - N - (*m* - acetamidophenyl) - thiocarbamate;
 O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N-methyl - N - (*m* - methylthiophenyl) - thiocarbamate.

EXAMPLE 5.

- Thiophosgene (1.15 g; 0.01 moles) in chloroform (40 ml) was slowly treated with sodium 1,4 - methano - 1,2,3,4 - tetrahydro-6-naphthoxide (1.82 g; 0.01 mole) at ambient temperature. After 30 minutes, the undissolved material was filtered off and the filtrate was evaporated to dryness to give O-(1,4-methano-1,2,3,4 - tetrahydro - 6 - naphthyl) - chlorothioformate (2.3 g; $n_D^{20} = 1.5930$). N-methyl-*m*-toluidine (2.42 g; 0.02 mole) was added dropwise to this compound in a little chloroform at ambient temperature. The reaction mixture was stirred for 48 hours at ambient temperature, then refluxed for two hours. The solvent was evaporated, and the residue redissolved in water and extracted repeatedly with diethyl ether. The organic phase was dried (Na_2SO_4) and evaporated to dryness to give, after crystallisation from isopropanol, O-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl) - N - methyl - N - (*m* - tolyl) - thiocarbamate (1.3 g) m.p. 92–94°C.
 By following the same method, the other compounds described in Examples 1 to 4 could be obtained.

EXAMPLE 6.

- Thiophosgene (0.115 g; 0.001 moles) in chloroform (20 ml) was treated dropwise with stirring with sodium 1,4-ethano-1,2,3,4-tetrahydro-6-naphthoxide (0.197 g; 0.001 mole). The mixture was then heated for 15 minutes at 30–40°C and cooled, the undissolved pro-

duct was filtered and the filtrate was added dropwise to a suspension of N-methyl-*m*-toluidine (0.121 g; 0.001 mole) and sodium bicarbonate (0.084 g; 0.001 mole) in ethanol, (30 ml). The mixture was stirred and cooled to 0 to 10°C. The mixture was kept for 30 minutes at 40–50°C, and then the solvent was evaporated. The residue was redissolved in water and extracted with chloroform. The organic extracts gave, after drying (CaCl_2), evaporation and crystallisation from ethanol/water, O-(1,4-ethano-1,2,3,4-tetrahydro-6-naphthyl) - N - methyl - N - (*m*-tolyl) - thiocarbamate (0.19 g), m.p. 110–112°C.

By following the same method, the other compounds described in Examples 1 to 4 could be obtained.

EXAMPLE 7.

m-Toluidine (1.07 g; 0.01 mole) in ethanol (10 ml) was treated with S-ethyl O-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-dithiocarbonate (2.64 g; 0.01 mole) in ethanol (20 ml) at room temperature. The mixture was kept for about 20 hours at 50°C and then evaporated to dryness, the residue gave, after repeated crystallisations from ethanol at 95°, O-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl) - N - (*m* - tolyl) - thiocarbamate (1.55 g), m.p. 115–118°C.

By following the same method, the other compounds described in Examples 1 to 4 could be obtained.

EXAMPLE 8.

1,4 - Methano - 1,2,3,4 - tetrahydro - 6-naphthyloxy formic 1,4 - methano - 1,2,3,4-tetrahydro - 6 - naphthyloxythio - formic thio anhydride [4.22 g; 0.01 mole, prepared by Holmberg's method (J. Prakt. Chem. 1905, 2, 71, 264)] in ethanol (~50 ml) was treated dropwise with aniline (2.0 g; 0.0215 mole) under stirring and cooling at 0°C. After stirring for three hours at ambient temperature, the reaction mixture was mildly acidified with 3N-hydrochloric acid, diluted in water, cooled and filtered. The precipitate thus obtained, after repeated recrystallisations from isopropanol, gave O-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl) - N - phenyl - thiocarbamate (1.4 g) m.p. 150–152°C.

The other compounds described in Examples 1 to 4 could be obtained by following the same method.

EXAMPLE 9.

1,4 - Methano - 1,2,3,4 - tetrahydro - 6-naphthol (16 g; 0.1 mole) in acetone (~100 ml) was treated with sodium carbonate (10.6 g; 0.1 mole). Then N-methyl-N-(*m*-tolyl)thiocarbamoyl/chloride (19.9 g; 0.1 mole) was added at ambient temperature. The mixture was stirred, refluxed for two hours, cooled and redissolved in water (~200 ml), and the solid

- product thus obtained was filtered, washed with water and crystallised from ligroin to give O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (m - tolyl) - thiocarbamate (12.9 g) m.p. 92—94° C.
- The other compounds of Examples 1 to 4 could be prepared by following the same method.

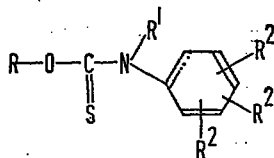
EXAMPLE 10.

- 1,4 - Methano - 1,2,3,4 - tetrahydro - naphth-6-ol (12 g; 0.075 mole) and phenyl isothiocyanate (10 g; 0.074 mole) were refluxed for 8 hours in dry benzene (100 ml), after addition of a few drops of triethylamine. Removal of the benzene under vacuum gave an oily residue which was then crystallised from isopropanol to give O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - phenyl thiocarbamate (8.9 g) m.p. 150—152° C.

- By following the same method, the other compounds described in Example 1 could be obtained and further the compounds described in Examples 3 and 4, wherein R₁ is a hydrogen atom, could be obtained.

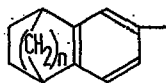
WHAT WE CLAIM IS:—

1. A compound of general formula (I)



I

- wherein R is a 5,6,7,8-tetrahydro-2-naphthyl group or a group of general formula



- wherein n is 1, 2 or 3, R¹ is a hydrogen atom or a C₁₋₈ alkyl group; and each of the groups R², which may be the same or different, is a hydrogen or halogen atom, a nitro, cyano, trihalomethyl, phenyl, C₁₋₈ alkyl or C₁₋₈ alkoxy group or a group of formula —SR³, —COR³ or —NHCOR³ wherein R³ is a C₁₋₈ alkyl group.

2. A compound according to claim 1 wherein R¹ and one of groups R² are methyl groups.

3. O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N - (m - tolyl) - thiocarbamate.

4. O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N - methyl - N - (m - tolyl) thiocarbamate.

5. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - phenyl - thiocarbamate.

6. O - (1,4 - methano - 1,2,3,4 - tetra-

- hydro - 6 - naphthyl) - N - (m - tolyl) - thiocarbamate.

7. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (m - methoxyphenyl) - thiocarbamate.

8. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (m - chlorophenyl) - thiocarbamate.

9. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (m - nitrophenyl) - thiocarbamate.

10. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (p - diphenyl) - thiocarbamate.

11. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (2 - methyl - 4 - chlorophenyl) - thiocarbamate.

12. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (2 - methoxy - 5 - nitrophenyl) - thiocarbamate.

13. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl - N - (m - trifluoromethyl-phenyl) - thiocarbamate.

14. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (m - acetyl-phenyl) - thiocarbamate.

15. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl - N - (m - methylthio-phenyl) - thiocarbamate.

16. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - phenyl - thiocarbamate.

17. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (m - tolyl) - thiocarbamate.

18. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (p - nitrophenyl) - thiocarbamate.

19. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl - N - methyl - N - (m - chlorophenyl) - thiocarbamate.

20. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl - N - methyl - N - (m - nitrophenyl) - thiocarbamate.

21. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl - N - methyl - N - (m - methoxyphenyl) - thiocarbamate.

22. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (p - tolyl) - thiocarbamate.

23. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (p - diphenyl) - thiocarbamate.

24. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - ethyl - N - phenyl - thiocarbamate.

25. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (m - trifluoromethylphenyl) - thiocarbamate.

26. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (m - acetylphenyl) - thiocarbamate.

27. O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (m - tolyl) - thiocarbamate.

product thus obtained was filtered, washed with water and crystallised from ligroin to give O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (m-tolyl) - thiocarbamate (12.9 g) m.p. 92—94° C.

The other compounds of Examples 1 to 4 could be prepared by following the same method.

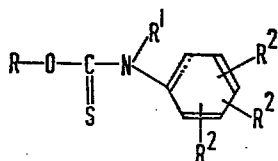
EXAMPLE 10.

1,4 - Methano - 1,2,3,4 - tetrahydro-naphth-6-ol (12 g; 0.075 mole) and phenyl isothiocyanate (10 g; 0.074 mole) were refluxed for 8 hours in dry benzene (100 ml), after addition of a few drops of triethylamine. Removal of the benzene under vacuum gave an oily residue which was then crystallised from isopropanol to give O-(1,4-methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - phenyl thiocarbamate (8.9 g) m.p. 150—152° C.

By following the same method, the other compounds described in Example 1 could be obtained and further the compounds described in Examples 3 and 4, wherein R₁ is a hydrogen atom, could be obtained.

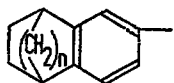
WHAT WE CLAIM IS:—

1. A compound of general formula (I)



I

wherein R is a 5,6,7,8-tetrahydro-2-naphthyl group or a group of general formula



wherein *n* is 1, 2 or 3, R¹ is a hydrogen atom or a C₁₋₆ alkyl group; and each of the groups R², which may be the same or different, is a hydrogen or halogen atom, a nitro, cyano, trihalomethyl, phenyl, C₁₋₆ alkyl or C₁₋₆ alkoxy group or a group of formula —SR³, —COR³ or —NHCOR³ wherein R³ is a C₁₋₆ alkyl group.

2. A compound according to claim 1 wherein R¹ and one of groups R² are methyl groups.

3. O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N-(m-tolyl)-thiocarbamate.

4. O - (5,6,7,8 - tetrahydro - 2 - naphthyl) - N-methyl-N-(m-tolyl)thiocarbamate.

5. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - phenyl - thiocarbamate.

6. O - (1,4 - methano - 1,2,3,4 - tetra-

hydro - 6 - naphthyl) - N - (m - tolyl) - thiocarbamate.

7. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (m - methoxyphenyl)-thiocarbamate.

8. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (m - chlorophenyl)-thiocarbamate.

9. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (m - nitrophenyl)-thiocarbamate.

10. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (p - diphenyl)-thiocarbamate.

11. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (2 - methyl) - 4-chlorophenyl)-thiocarbamate.

12. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (2 - methoxy-5-nitrophenyl)-thiocarbamate.

13. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (m - trifluoromethyl-phenyl)-thiocarbamate.

14. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (m - acetylphenyl)-thiocarbamate.

15. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (m - methylthiophenyl)-thiocarbamate.

16. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N-phenyl-thiocarbamate.

17. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (m-tolyl)-thiocarbamate.

18. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (p-nitrophenyl)-thiocarbamate.

19. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (m-chlorophenyl)-thiocarbamate.

20. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (m-nitrophenyl)-thiocarbamate.

21. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (m-methoxyphenyl)-thiocarbamate.

22. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (p-tolyl)-thiocarbamate.

23. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (p-diphenyl)-thiocarbamate.

24. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - ethyl - N - phenyl-thiocarbamate.

25. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (m-trifluoromethylphenyl)-thiocarbamate.

26. O - (1,4 - methano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (m-acetylphenyl)-thiocarbamate.

27. O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - (m - tolyl) - thiocarbamate.

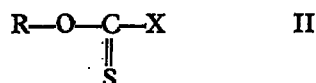


28. O - (1,4 - ethano - 1,2,3,4 - tetrahydro - 6 - naphthyl) - N - methyl - N - (m-tolyl)-thiocarbamate.

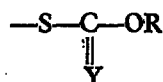
29. A compound according to claim 1 wherein R^2 is as defined in claim 1 except that when R^2 is a trihalomethyl group it is a trifluoromethyl group.

30. A process for preparing a compound according to any one of the preceding claims, the process comprising

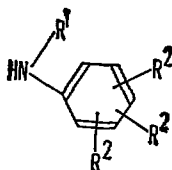
10 (a) reacting a compound of general formula (II)



15 wherein R is as defined in claim 1, and X is a halogen atom, a group of formula $-\text{S}-\text{R}^4$ wherein R^4 is an alkyl or substituted or unsubstituted phenyl group, or a group of formula



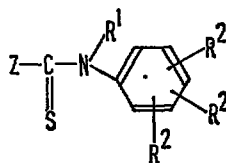
20 wherein R is as defined in claim 1 and Y is an oxygen or sulphur atom, with an amine of general formula (III)



III

25 wherein R^1 and R^2 are as defined in claim 1; or

(b) reacting a compound of general formula (IV)



IV

wherein R^1 and R^2 are as defined in claim 1 and Z is a halogen atom, with a compound of general formula (V)

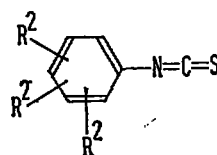


wherein R is as defined in claim 1 and M is a hydrogen or metal atom; or

(c) reacting a compound of general formula (VI)



wherein R is as defined in claim 1, with a compound of general formula (VII)



VII

wherein R^2 is as defined in claim 1, to give a compound of general formula (I) wherein R^1 is a hydrogen atom.

31. A process according to claim 30 substantially as described in any one of the Examples.

32. A compound of general formula (I) prepared by a process according to claim 30 or 31.

33. A pharmaceutical composition comprising a compound according to any one of claims 1, 2, 4, 6 to 16, 18 to 27 and 32, and a pharmaceutically acceptable carrier or diluent.

34. A composition according to claim 33 substantially as described herein.

35. A pharmaceutical composition comprising a compound according to any one of claims 3, 5, 17, 28 and 29, and a pharmaceutically acceptable carrier or diluent.

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