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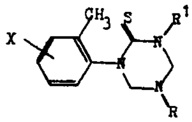
(54) **Tetrahydro-s-triazine thiones, process for their preparation and acaricidal compositions containing them.**

(57) Tetrahydro-s-triazine thiones, process for their preparation and acaricidal compositions containing them.
Compounds of formula:



wherein R is alkyl, cycloalkyl, adamantyl, lower alkenyl, or a lower-alkynyl or a substituted-lower alkyl wherein the substituent is hydroxy, lower alkoxy, lower alkanoyloxy, carbamoyloxy, N-lower alkyl-carbamoyloxy, N-cycloalkyl-carbamoyloxy, N-aryl-carbamoyloxy, thiocarbamoyloxy, N-lower alkyl-thiocarbamoyloxy, N-cycloalkylthiocarbamoyloxy, N-aryl-thiocarbamoyloxy, aryl-sulphonyloxy, mono- or di-lower alkyl-amino or aryl;
R^1 is lower alkyl or hydroxy-methyl;
and X is hydrogen or lower alkyl;
and acid addition salts thereof.

A process for their preparation and acaricidal compositions.

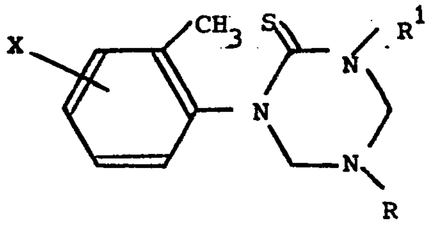
EP 0 000 640 A1

Croydon Printing Company Ltd.

This invention relates to a series of tetrahydro-s-triazine thiones having useful pesticidal properties. In particular, the compounds are effective in destroying one or more stages in the life cycle of ticks which tend to infest the skins of animals such as sheep and cattle, and are therefore especially useful as ectoparasiticidal agents for treating such animals. They also have insecticidal properties, particularly against plant insects such as pea aphids.

All stages in the life cycle of the ticks tend to damage the skins of afflicted animals and thereby spoil the state of the skins, with the consequence, for example, that cattle hides and sheep skins intended for the manufacture of leather and sheep skin, respectively, are reduced in quality. Furthermore, the ticks may facilitate the transmission of disease to the afflicted animal, and the general state of health and the quality of flesh of the animal may be detrimentally affected.

The present invention therefore provides novel tetrahydro-s-triazin-2[1H]-thiones of the general formula:-



--- (I)

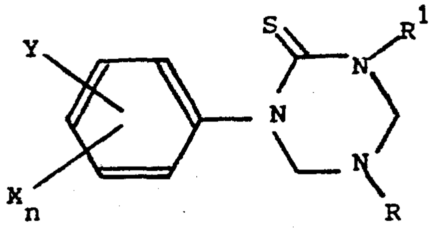
wherein R is an alkyl, cycloalkyl, adamantyl, lower alkenyl or lower alkynyl group or a substituted-lower alkyl group wherein the substituent is a hydroxy, alkoxy, lower alkanoyloxy, carbamoyloxy, N-lower alkyl-carbamoyloxy, N-cycloalkyl-carbamoyloxy, N-arylcarbamoyloxy, thiocarbamoyloxy, N-lower alkyl-thiocarbamoyloxy, N-cycloalkyl-thiocarbamoyloxy, N-aryl-thiocarbamoyloxy, aryl-sulphonyloxy, mono or di-lower alkylamino or an aryl group;

R^1 is a lower alkyl or hydroxy- methyl group; and X is a hydrogen atom or a lower alkyl group;
and acid addition salts thereof.

In this specification the term "lower" applied to a substituent group means that it contains up to six carbon atoms: groups containing three or more carbon atoms may be straight or branched chain. When R is an alkyl group, it may contain up to twelve carbon atoms. Halogen means fluorine, chlorine, bromine or iodine. Aryl means a phenyl group which may optionally be substituted with one or more halogen atoms or lower alkyl, lower alkoxy, trifluoromethyl, cyano or hydroxy groups.

One preferred group of compounds according to the invention comprises compounds of the formula (I) wherein X is a lower alkyl group, particularly a methyl group at the 4- position. Also preferred are compounds of the formula (I) wherein R^1 is a lower alkyl group, particularly a methyl group and R is a lower alkyl group, particularly a methyl, isopropyl or t-butyl group, or a cyclohexyl or hydroxyethyl group. Particularly preferred individual compounds of the invention include: 1-(2,4-dimethylphenyl)-3,5-dimethyl-tetrahydro-s-triazin-2[1H]-thione; 1-(2,4-dimethylphenyl)-3-methyl-5-isopropyl-tetrahydro-s-triazine-2[1H]-thione and 1-(2,4-dimethylphenyl)-3-methyl-5-t-butyl-tetrahydro-s-triazine-2[1H]-thione.

Compounds of the formula:-

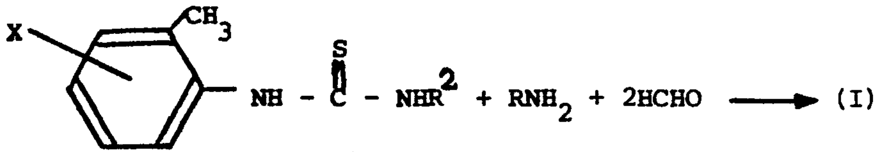


--- (IA)

wherein R^1 is alkyl; R is alkyl, cycloalkyl, alkenyl, alkynyl or hydroxyalkyl; X is hydrogen or halogen; Y is hydrogen, halogen or alkyl; and n is 1 or 2;

are disclosed in United States Patent Nos. 3505057 and 3505323 as herbicidal compounds, but there is no disclosure therein of compounds of the formula (I) above in which there is a methyl group at the 2-position of the phenyl group, nor is there any disclosure therein that compounds of the formula (IA) have acaricidal or insecticidal properties.

The compounds of the formula (I) where R^1 is lower alkyl may be prepared from a substituted thiourea of the formula (II) and an amine RNH_2 i the presence of formaldehyde according to the following equation:-



(II)

where R and X are as previously defined and R^2 is lower alkyl.

The reaction is generally performed in the presence of an aqueous organic solvent, e.g. aqueous dioxan, aqueous propanol or aqueous ethylene glycol and may conveniently be carried out by adding the amine to excess aqueous formaldehyde solution and then adding the thiourea, preferably as a solution in an organic solvent e.g. dioxan. The reaction may be performed at a temperature between room temperature and the reflux temperature of the solvent and may take from several hours to several days to complete depending on the nature of the reactants and the temperature employed. We have found that the reaction is preferably performed at a temperature of 45-50°C to avoid the decomposition and formation of bi-products which sometimes occurs at higher temperatures, and generally takes two or three days to go substantially to completion at this temperature.

In other cases, for example, where R^2 and R are lower alkyl groups (e.g. methyl groups) the reaction can with advantage be performed at a higher temperature e.g. by heating on a steam bath, and in this case the reaction is generally complete within 1½ to 3 hours. In some instances the product crystallises on cooling the solution otherwise the product is conveniently isolated by evaporation of the solvent or alternatively by adding a large excess of water to precipitate the product which is collected by filtration or by extraction into an organic solvent, e.g. diethyl ether, and removal of the solvent. In either case the crude product may be further purified, if desired, by conventional techniques, e.g. by recrystallisation or by chromatography. Compounds of the formula (I) wherein R is a lower alkyl group substituted with a lower alkanoyloxy group may also be prepared by acylation of the corresponding hydroxy-lower alkyl substituted compound e.g. using the acid chloride. Compounds of the formula (I) wherein R is a lower alkyl group substituted with a carbamoyloxy, thiocarbamoyloxy or N-substituted-carbamoyloxy or thiocarbamoyloxy group may similarly be prepared from the corresponding hydroxy-lower alkyl substituted compound using potassium isocyanate or isothiocyanate or an appropriate lower alkyl, cycloalkyl or aryl isocyanate or isothiocyanate respectively. Compounds of the formula (I) wherein R is a lower alkyl group substituted with an aryl-sulphonyloxy group may also be prepared from the corresponding hydroxy-lower alkyl compound sulphonylation, e.g. using a sulphonyl chloride.

Compounds of the formula (I) wherein R^1 is a hydroxy-methyl group may be prepared from the compound of the formula (I) wherein R^1 is hydrogen, prepared as indicated above using a thiourea of the formula (II) wherein R^2 is hydrogen. Thus, reaction with formaldehyde yields the compound of formula (I) wherein R^1 is a hydroxy-methyl group.

The acid-addition salts of the compounds of the formula (I) may be made in a conventional manner, e.g. by mixing a solution of the free base in a suitable solvent, e.g. diethyl ether, with a solution of the appropriate acid, e.g. hydrochloric acid, in a suitable solvent, e.g. diethyl ether, and recovering the salt as a precipitate.

The starting thioureas of formula (II) are known compounds or they may be readily prepared by conventional reactions. For example the preparation of the compound of formula (II) wherein R^2 and X are each a methyl group is described in J. Chem. Soc., (1929) 945. Other compounds of formula (II) may be prepared in a similar manner by reaction of an appropriately ring substituted aniline derivative with an alkyl isothiocyanate. If desired, the starting thiourea need not be isolated but the crude reaction mixture may be treated directly with formaldehyde and the amine of formula RNH_2 to give the final product of formula (I) in a single step.

The amines of formula RNH_2 are all readily available compounds.

The compounds of the formula (I) have acaricidal activity, particularly against all stages in the life cycle, including gravid female ticks, of the cattle ticks Boophilus microplus, Haemaphysalis longicornus, Rhipicephalus appendiculatus and Boophilus decoloratus.

In one test, five freshly collected, fully engorged Boophilus microplus adult female ticks are used for each acaricidal compound. Using a micro-pipette 10 micro-litres of a solution containing 10 micro-grams of the acaricidal compound in ethanol or acetone, is applied to the dorsal surface of each of the ticks. The treated ticks are placed in weighed 1" x 2" glass vials, weighed and stored at 26°C and 80% relative humidity in plastic boxes for two weeks. The ticks are then removed from the vials and the vials weighed to give the weight of eggs laid by the ticks. Any reduction in the egg laying of the treated ticks is calculated as a percentage of the eggs laid by untreated control ticks.

The eggs are returned to the incubator for a further 3 weeks after which time the percentage of eggs hatching is estimated. The percentage effect is calculated as the overall reduction in the anticipated reproduction of the ticks using the weight of eggs laid and the percentage of eggs hatching. The test may be repeated using smaller amounts of the acaricidal compound.

In another test, using a pipette 0.5 ml of a solution containing 0.5 mg of the acaricidal compound in ethanol or acetone is spread evenly on to a Whatman No. 1 filter paper 8 cm x 6.25 cm (50 sq. c.m.) to give a dosage of 100 mg/m^2. The treated paper is allowed to dry at room temperature, folded with the treated surface inside and two short edges sealed with a crimping machine.

The open ended envelope is placed in a 1lb Kilner jar containing damp cotton wool in a plastic pot and stored in an incubator at 26°C for 24 hours. 20 - 50 Boophilus microplus larvae, which had hatched 8 - 14 days previously, are placed in the envelope using a small spatula. The open end is then crimped to form a sealed packet. The treated paper containing the larvae is returned to the Kilner jar and kept for a further 48 hours in the incubator. 20 - 50 larvae are placed similarly in an untreated paper envelope to act as controls. At the end of the 48 hour test period the mortality is noted and recorded as a percentage after correction for any mortality among the untreated control ticks.

The test may be repeated using smaller amounts of the acaricidal compound.

In addition to percentage effectiveness figures, ED_{50} results can be obtained from dose response measurements using any of the afore-described tests.

Activity against Haemaphysalis longicornus nymphs may be measured in a similar manner to the above larvae test.

The activity of certain of the compounds of the Examples detailed hereinafter against the tick Boophilus microplus is set out in the following Table:-

TABLE I

Acaricidal activity vs. Adult Boophilus microplus

(topical application)

Example No.	% Effect at 10 µg
1	100
2	99
3	100
4	100
5	100
6	100
7	99
8	68
9	86
10	100
11	100
12	95
13	58
14	100
15	28
16	78
17	93
18	94
19	74
20	63
21	47
22	100
23	89
24	10
25	49
26	25
27	100
28	80
29	35

Thus the invention also provides an acaricidal composition comprising an effective amount of a compound of the formula (I) together with a diluent or carrier. The diluent or carrier may be a solid or a liquid, optionally together with an antioxidant, dispersing agent, emulsifying agent or wetting agent. The compositions of the invention include not only compositions in a suitable form for application but concentrated primary compositions which may be supplied to the user and which require dilution with a suitable quantity of water or other diluent prior to application. Typical compositions of the invention include, for example, dusting powders, dispersible powders, solutions, dispersions, emulsions and emulsifiable concentrates.

A dust may be made by mixing the appropriate amount of the finely divided active compound with a solid pulverulent diluent or carrier such as talc, clay, calcite, pyrophyllite, diatomaceous earth, walnut shell flour, silica gel, hydrated alumina, or calcium silicate. As an alternative method of preparation, the diluent or carrier is mixed with a solution of the active compound in a volatile organic solvent such as toluene, the solvent being subsequently removed by evaporation. Typically, the active compound will be present in the dust in an amount of from 0.25 to about 4% by weight.

Dispersible powders of special value for spray applications may be made by adding a suitable dispersing agent to the active compound, or to a dust containing the active compound, so that a stable aqueous dispersion of the active compound is formed on mixing the powder with water. The dispersible powders preferably contain from about 25 to 75% by weight of the active compound.

Emulsifiable concentrates comprise a solution of the active compound in a substantially water-immiscible non-toxic organic solvent containing an emulsifying agent. Suitable solvents include, for example, toluene, xylene, petroleum oil, and alkylated naphthalenes. Preferably, the concentrate will contain 5-75 gms. of the active compound per 100 ml. of solution. The concentrates may be diluted with water prior to use to give a typical concentration of the active compound in the aqueous medium of from e.g. about 0.01 to about 0.1% w/v (g/100 ml), or approximately 100 to 1000 p.p.m. The volatile solvents, e.g. toluene and xylene, evaporate after spraying to leave a deposit of the active ingredient. The made up spray or dip will generally be an emulsion.

The compositions of the invention may be applied to ground, such as that around dairies, in order to combat e.g. cattle ticks, thereon. However, it is preferred to treat animals by spraying them or passing them through animal dips.

Thus the present invention also provides a method for protecting animals , particularly cattle, from acarids, particularly cattle ticks, which comprises treating the animal externally with an acaricidal amount of a compound of the formula (I) or acaricidal composition as defined above.

The compositions of the invention may also contain a pesticide, fungicide, additional acaricide, or the like.

The invention is illustrated by the following Examples.

EXAMPLE 1

t-Butylamine (0.88 g, 12 mmole) was added dropwise with stirring to a cooled 37% solution of aqueous formaldehyde (20 ml). After 15 minutes a warm solution of N-2,4-dimethylphenyl N'-methyl thiourea (1.94 g, 10 mmole) in dioxan (5 ml) was added and the mixture was warmed at 45 to 50°C for 48 hours. The solvent was removed by evaporation under reduced pressure to yield an oil which was washed with water and then extracted with methylene chloride (2 x 50 ml). The extracts were combined, dried over $MgSO_4$ and evaporated. The residue was taken up in diethyl ether (20 ml) and cooled to yield a crystalline precipitate which was collected by filtration, washed with a little cold hexane and dried under vacuum to give 5-t-butyl-1-(2,4-dimethylphenyl)-3-methyl-tetrahydro-s-triazin-2[1H]-thione as a white crystalline solid (1.35 g, 46%), m.p. 111-112°C. Found: C, 66.4, H, 9.0, N, 14.6%. $C_{16}H_{25}N_3S$ requires: C, 66.0, H, 8.6, N, 14.4%. $^{m}/e$ found 291, required 291.

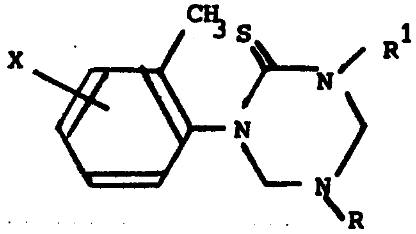
EXAMPLE 2

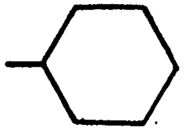
A solution of 2,4-xylidine (121 g, 90% purity) in ethylene glycol (195 ml) was added over five minutes to a mixture of methylisothiocyanate (73 g) in ethylene glycol (195 ml) and the mixture was stirred and heated on a steam bath for ½ hour. Aqueous formaldehyde solution (330 ml of 37%) was then added over five minutes followed by aqueous methylamine solution (230 ml of 25% weight/volume) and the reaction mixture was again stirred and heated on the steam bath for a further 1½ hours.

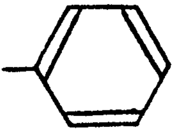
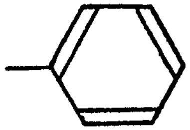
The resulting clear solution was allowed to cool to room temperature with stirring, the resulting crystalline precipitate was collected by filtration, washed with water and dried. Recrystallisation from chloroform/hexane gave 1-(2,4-dimethylphenyl)-3,5-dimethyl-tetrahydro-s-triazin-2[1H]-thione (200 g, 87% yield), m.p. 107-108°C. Found: C, 62.7, H, 7.7, N, 17.0. $C_{13}H_{19}N_3S$ requires C 62.3, H, 7.6, N, 16.9%. $^m/e$ found 249, required 249.

EXAMPLES 3 - 20

The following tetrahydro-s-triazin-2[1H]-thiones were prepared by the general method of Example 1 starting with the appropriate thiourea and amine.



Example No.	R^1	R	X	m.p. °C	Analysis % (Theoretical in brackets)		
					C	H	N
3	CH_3	CH_2CH_2OH	4-CH_3	101-2	60.1 (60.2	7.55 7.5	14.9 15.1)
4	CH_3	$CH(CH_3)_2$	4-CH_3	113-4	64.8 (65.0	8.3 8.3	15.1 15.2)
5	CH_3		4-CH_3	100-1	68.1 (68.1	8.6 8.5	13.4 13.3)
6	CH_3	CH_2CH_3	4-CH_3	oil	63.1 (63.9	8.1 8.0	15.3 16.0)
7	CH_3	$CH_2CH{=}CH_2$	4-CH_3	76-7	65.6 (65.4	7.9 7.6	15.0 15.3)

Example No.	R^1	R	X	m.p. ^oC	Analysis % (Theoretical in brackets)		
					C	H	N
8	CH_3	CH_2 	4-CH_3	124-5	70.4 (70.1	7.4 7.1	13.2 12.9)
9	CH_2CH_3	CH_3	4-CH_3	78-9	63.6 (63.9	8.0 8.0	15.9 16.0)
10	CH_3	CH_2CH_2 	4-CH_3	glass	70.5 (70.8	7.3 7.4	12.7 12.4)
11	CH_3	$(CH_2)_3CH_3$	4-CH_3	oil	66.0 (65.6	8.6 9.1	14.4 14.4)

Example	R^1	R	X	m.p. °C	Analysis % (Theoretical in brackets)		
					C	H	N
12	CH_3	CH_3	H	120-1	60.8 (61.2	7.5 7.3	18.1 17.9)
13	CH_3	CH_3	3-CH_3	186-7	62.4 (62.6	7.8 7.7	16.9 16.9)
14	CH_3	CH_3	6-CH_3	121-2	62.7 (62.6	7.9 7.7	17.1 16.9)
15	CH_2CH_3	CH_2CH_3	4-CH_3	oil	m/e = 277		
16	CH_3	$(CH_2)_{11}CH_3$	4-CH_3	oil	71.5 (71.5	10.4 10.2	10.7 10.4)
17	CH_3	$(CH_2)_9CH_3$	4-CH_3	oil	70.25 (70.4	10.0 9.9	11.6 11.2)
18	CH_3	adamantyl	4-CH_3	151-2	71.4 (71.2	8.6 8.9	11.3 11.3)
19	CH_3	$(CH_2)_5CH_3$	4-CH_3	oil	67.6 (67.7	9.5 9.1	13.2 13.2)
20	CH_3	$(CH_2)_3OH$	4-CH_3	110-115	60.6 (61.4	7.7 7.8	13.0 14.3)

EXAMPLE 21

Formaldehyde (4.86 g, 37% solution, 30 mmole) was added to a solution of 2,4-dimethyl-phenyl thiourea (4.5 g, 24 mmole) in dimethylformamide (40 ml) and the solution was stirred for 15 minutes at room temperature. Methylamine (3.72 g, 30 mmole) was added dropwise with stirring and the mixture was heated under reflux at 100°C for 4 hours. The solution was cooled and the solvent removed under vacuum to yield an oil. This was diluted with diethylether and refrigerated to yield 1-(2,4-dimethylphenyl)-5-methyl-tetrahydro-s-triazin-2[1H]-thione as a white crystalline solid which was collected, washed with a little cold diethyl ether and dried (4.5 g, 77%), m.p. 140 - 143°C.

The product (1.18 g, 5 mmole) was dissolved in dioxan (5 ml) with warming, the solution cooled to room temperature and formaldehyde (0.41 g, 37% solution, 5 mmole) added. The solution was kept at 45°C for 6 weeks. The solvent was then removed under vacuum and the product was washed with water, dissolved in dichloromethane, dried over $MgSO_4$ and the solvent evaporated to yield a clear oil which solidified on stirring with diethyl ether (50 ml). The product was recrystallised from a mixture of hexane and dichloromethane to yield 1-(2,4-dimethylphenyl)-3-hydroxymethyl-5-methyl-tetrahydro-s-triazin-2[1H]-thione as a white crystalline solid (0.40 g, 30%), m.p. 121 - 122°C.

Analysis %:-

Found:	C, 58.5;	H, 7.1;	N, 15.65
$C_{13}H_{19}N_3OS$ requires:	C, 58.9;	H, 7.2;	N, 15.85%.

EXAMPLE 22

Acetyl chloride (0.168 g, 1.5 mmole) was added dropwise with stirring to a cooled solution of 1-(2,4-dimethylphenyl)-5-(2-hydroxyethyl)-3-methyl-tetrahydro-s-triazin-2[1H]-thione (0.60 g, 1 mmole) in dry toluene (45 ml) containing triethylamine (0.3 g, 3 mmole). After 10 minutes the solution was allowed to warm to room temperature and stirring was continued for a further 3 hours. The solution was filtered and the solvent removed under vacuum. The product was chromatographed on a column of silica eluting with dichloromethane containing 2% methanol to yield an oil. Trituration with diethyl ether gave 5-(2-acetoxyethyl)-1-(2,4-dimethylphenyl)-3-methyl-tetrahydro-s-triazin-2[1H]-thione. (0.24 g, 35%), m.p. 80 - 83°C.

Analysis %:-

Found:	C, 59.7; H, 7.3; N, 12.95
$C_{16}H_{23}N_3O_2S$ requires:	C, 59.8; H, 7.2; N, 13.1%.

EXAMPLE 23

The method of Example 22 was followed using pivaloyl chloride to give 1-(2,4-dimethylphenyl)-3-methyl-5-(2-pivaloyloxy ethyl)-tetrahydro-s-triazin-2[1H]-thione as an oil.

Analysis %:-

Found:	C, 62.35; H, 8.1; N, 10.9
$C_{19}H_{29}N_3O_2S$ requires:	C, 62.8; H, 8.0; N, 11.6%

EXAMPLE 24

Phenylisocyanate (0.62 g, 5.2 mmole) was added to a stirred solution of 1-(2,4-dimethylphenyl)-5-(2-hydroxyethyl)-3-methyl-tetrahydro-s-triazin-2[1H]-thione (1.0 g, 3.5 mmoles) and triethylamine (0.31 g, 5.2 mmole) in dry toluene (40 ml). The mixture was stirred at room temperature for 2 hours and the solvent was then removed under vacuum and the residual gum triturated with petroleum ether (b.p. 60 - 80°C) to yield 1-(2,4-dimethylphenyl)-3-methyl-5-(2-N-phenyl-carbamoyloxyethyl)-tetrahydro-s-triazin-2[1H]-thione (1.18 g, 84%), m.p. 60 - 65°C.

Analysis %:-

Found:	C, 64.0;	H, 6.6;	N, 13.5
$C_{21}H_{26}N_4O_2S$ requires:	C, 63.3;	H, 6.5;	N, 14.1.

EXAMPLE 25

The method of Example 24 was followed using methylisocyanate to give 1-(2,4-dimethylphenyl)-3-methyl-5-(2-N-methyl-carbamoyloxy ethyl)-tetrahydro-s-triazin-2[1H]-thione, m.p. 110-113°C.

Analysis %:-

Found:	C, 57.0;	H, 7.2;	N, 16.8
$C_{16}H_{24}N_4O_2S$ requires:	C, 57.1;	H, 7.1;	N, 16.7%

EXAMPLE 26

A solution of 1-(2,4-dimethylphenyl)-5-(2-hydroxyethyl)-3-methyl-tetrahydro-s-triazin-2[1H]-thione (1.0 g, 3.6 mmole) in dimethylformamide (10 ml) was added slowly to a stirred suspension of sodium hydride (0.172 g, 3.6 mmole as 50% dispersion in oil) at room temperature.

When evolution of hydrogen had ceased a solution of cyclohexyl isothiocyanate (0.74 g, 5.3 mmole) in dimethylformamide (5 ml) was added slowly and the mixture was stirred at room temperature for 3 hours. The solution was then poured into water (50 ml) and the product extracted into ether. The ether layer was separated, washed with water, dried and the solvent removed to yield an oil. Trituration with petroleum ether (b.p. 60 - 80°C) gave 5-(2-N-cyclohexylthiocarbamoyloxyethyl)-1-(2,4-dimethylphenyl)-3-methyl-tetrahydro-s-triazin-2[1H]-thione as a white solid (0.18 g, 12%), m.p. 68 - 72°C.

Analysis %:-

Found: C, 59.8; H, 7.7; N, 13.1

$C_{21}H_{32}N_4OS_2$ requires: C, 60.1; H, 7.4; N, 13.4.

EXAMPLE 27

The method of Example 26 was followed using methyl isothiocyanate to give 1-(2,4-dimethylphenyl)-3-methyl-5-(2-N-methylthiocarbamoyloxyethyl)-tetrahydro-s-triazin-2[1H]-thione, m.p. 82 - 90°C.

Analysis %:-

Found: C, 55.1; H, 7.0; N, 15.3

$C_{16}H_{24}N_4OS_2$ requires: C, 54.5; H, 6.8; N, 15.9.

EXAMPLE 28

The method of Example 26 was followed using phenyl isothiocyanate to give 1-(2,4-dimethylphenyl)-3-methyl-5-(2-N-phenylthiocarbamoyloxyethyl)-tetrahydro-s-triazin-2[1H]-thione, m.p. 64 - 70°C.

Analysis %:-

Found: C, 61.6; H, 6.3; N, 13.7

$C_{21}H_{26}N_4OS_2$ requires: C, 60.9; H, 6.3; N, 13.5.

EXAMPLE 29

A solution of p-toluenesulphonyl chloride (3.0 g) in pyridine (5 ml) was added slowly to a cold stirred solution of 1-(2,4-dimethylphenyl)-5-(2-hydroxyethyl)-3-methyl-tetrahydro-s-triazin-2[1H]-thione (1.5 g, 1.8 mmole) in pyridine (10 ml). Stirring was continued for a further 10 minutes and the solution was allowed to stand overnight at 3°C. The solution was poured into ice/water (400 ml) and the product extracted into ether (2 x 100 ml). The combined ethereal extracts were washed with dilute hydrochloric acid and with water and dried. The solvent was removed and the residual gum was taken up in ethyl acetate. The solution was chilled and petroleum ether (b.p. 40 - 60°C) added slowly to give 1-(2,4-dimethylphenyl)-3-methyl-5-(p-toluenesulphonyloxyethyl)-tetrahydro-s-triazin-2[1H]-thione as a white solid (0.9 g, 58%), m.p. 82 - 85°C.

Analysis %:-

Found:	C, 58.4; H, 6.3; N, 9.6
$C_{21}H_{27}N_3S_2O_3$ requires:	C, 58.2; H, 6.2; N, 9.7%

EXAMPLE 30

Aqueous formaldehyde (3.6 g, 4 mmole) was added to a suspension of N-2,4-dimethylphenyl-N'-methyl-thiourea (1.94 g, 2 mmole) in ethylene glycol (500 ml) followed by slow addition of a solution of N,N-dimethyl-ethylenediamine (1.76 g, 2 mmole) in a little ethylene glycol. The mixture was heated for 1 hour at 80 - 90°C and then cooled and poured into water. The product was extracted into ether, the ether layer separated, washed with water, dried and evaporated.

The crude product was chromatographed on a column of silica eluting with dichloromethane containing 3% methanol to yield an oil which solidified on trituration with petroleum ether (b.p. 40 - 60°C) to give 1-(2,4-dimethylphenyl)-3-methyl-5-dimethylaminoethyl-tetrahydro-s-triazin-2[1H]-thione (0.6 g, 20%), m.p. 65 - 70°C.

Analysis %:-

Found:	C, 62.25; H, 8.6; N, 17.8
$C_{16}H_{26}N_4S$ requires:	C, 62.7; H, 8.5; N, 18.3%.

EXAMPLE 31

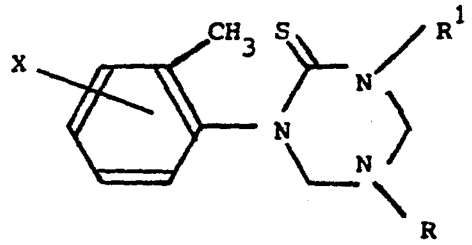
A solution of hydrogen chloride in ether was added to an ether solution of 1-(2,4-dimethylphenyl)-3,5-dimethyl-tetrahydro-s-triazin-2[1H]-thione. The mixture was allowed to stand in the cold for 1 hour and the precipitated hydrochloride salt was collected, washed with a little cold ether and dried, m.p. 164 - 165°C.

Analysis %:-

Found:	C, 54.45; H, 7.6; N, 15.2; Cl, 12.6
$C_{13}H_{19}N_3S.HCl$ requires:	C, 54.6; H, 7.0; N, 14.7; Cl, 12.4%.

CLAIMS

1. Compounds of the formula:



--- (I)

wherein R is an alkyl, cycloalkyl, adamantyl, lower alkenyl, or a lower-alkynyl group or a substituted-lower alkyl group wherein the substituent is a hydroxy, lower alkoxy, lower alkanoyloxy, carbamoyloxy, N-lower alkyl-carbamoyloxy, N-cycloalkyl-carbamoyloxy, N-aryl-carbamoyloxy, thiocarbamoyloxy, N-lower alkyl-thiocarbamoyloxy, N-cycloalkyl-thiocarbamoyloxy, N-aryl-thiocarbamoyloxy, aryl-sulphonyloxy, mono- or di-lower alkyl-amino or an aryl group;

R^1 is a lower alkyl or hydroxy-methyl group;

and X is a hydrogen atom or a lower alkyl group;

and acid addition salts thereof.

2, Compounds of the formula (I) as claimed in claim 1 wherein R is an alkyl, cycloalkyl, lower alkenyl, lower alkynyl, hydroxy-lower alkyl or an aryl-lower alkyl group and R^1 and X are as defined in claim 1.

3. Compounds as claimed in claim 1 or 2 wherein X is a lower alkyl group.

4. Compounds as claimed in claim 3 wherein X is a methyl group in the 4- position.

5. Compounds as claimed in any preceding claim wherein R^1 is a methyl group.

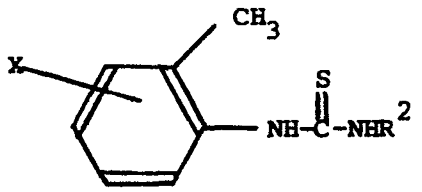
6. Compounds as claimed in any preceding claim wherein R is a methyl, isopropyl or t-butyl group.

7. 3-(2,4-Dimethylphenyl)-1,5-dimethyl-tetrahydro-s-triazin-2[1H]-thione,

3-(2,4-Dimethylphenyl)-1-methyl-5-isopropyl-tetrahydro-s-triazin-2[1H]-thione, or

3-(2,4-Dimethylphenyl)-1-methyl-5-t-butyl-tetrahydro-s-triazin-2[1H]-thione.

8. A process for preparing a compound of the formula (I) as defined in claim 1 which comprises reaction of a thiourea of the formula:



--- (II)

wherein R^2 is hydrogen or lower alkyl and X is as defined in claim 1; with an amine of the formula RNH_2, where R is as defined in claim 1, in the presence of formaldehyde; optionally acylating, sulphonylating or reacting with potassium isocyanate or isothiocyanate or with a lower alkyl, cycloalkyl or an aryl isocyanate or isothiocyanate the compound formed when R is a hydroxy-lower alkyl group; and, in the case where R^2 is hydrogen reacting the product with formaldehyde; and, if desired forming the acid addition salt of the product.

9. An acaricidal composition comprising an effective amount of a compound of the formula (I) as claimed in any one of claims 1 to 7 together with a diluent or carrier.

European Patent Office

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EUROPEAN SEARCH REPORT

Application number

EP 78 30 0162

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
DA	US - A - 3 505 057 (R.W.LUCKENBAUGH) * Claim 1 * —	1,9
DA	US - A - 3 505 323 (R.W.LUCKENBAUGH) * Claim 1; column 1, abstract * —	1,9

CLASSIFICATION OF THE APPLICATION (Int. Cl.²)

C 07 D 251/08
A 01 N 9/22

TECHNICAL FIELDS SEARCHED (Int.Cl.²)

C 07 D 251/08
A 01 N 9/22

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	27-10-1978	STOOS

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