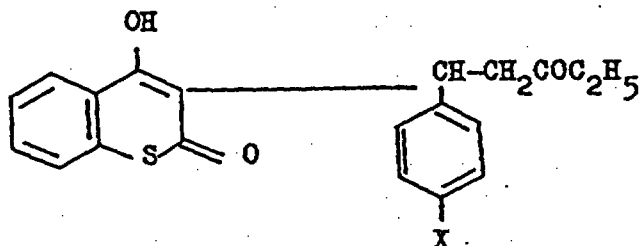


Description

-1-

The present invention relates to 4-hydroxy-2H-1-benzothiopyran-2-ones of formula (I), the preparation thereof and the compositions containing them.

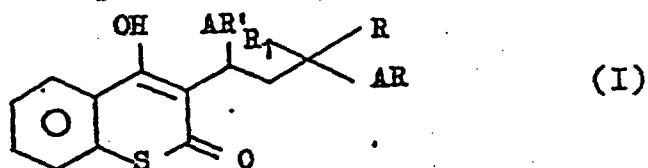
The interest of certain 1-thio-4-hydroxycoumarine derivatives is known, particularly from French Patent 2,351,653, which has for its object the compounds corresponding to the general formula



in which X designates a hydrogen, chlorine or bromine atom or a nitro group; and the medicament with anticoagulating activity in which the active principle formed by a 1-thio-4-hydroxy coumarine derivative is associated with a medium which can be administered therapeutically.

New compounds have been investigated, which in particular are substituted by a biphenyl or phenoxyphenyl group with anticoagulating activity, capable of constituting the active principle of a rodenticidal composition, permitting the application of an antidotal therapeutic in respect of non-rodent animals.

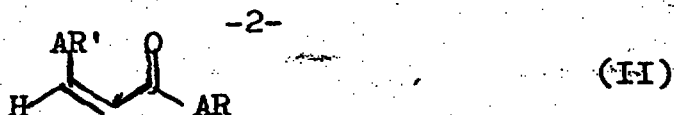
These compounds are represented by the formula:



in which: R may form, with AR', a tetrahydronaphthyl ring, when R₁ is hydrogen; R and R₁ may be a carbonyl group with the adjacent carbon atom; R may be a hydroxyl group when R₁ is hydrogen; AR is a biphenyl or phenoxyphenyl group, possibly substituted by a halogen; and AR' is a phenyl or thienyl group or may form, with R, a tetrahydronaphthyl ring, when R₁ is hydrogen.

They may be prepared in accordance with one or other of the following methods.

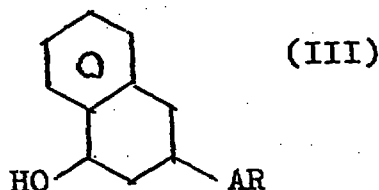
When RR₁ = 0 in the formula (1), the products are obtained by causing the reaction of 4-hydroxy-2H-1-benzothiopyran-2-one with compounds of the formula:



in a solvent such as ethanol, dioxane, in the presence of a condensation agent such as piperidine, at boiling point for several hours.

When $R = H$ and $R_1 = OH$ in the formula (I), the compounds are obtained by reducing, with the aid of sodium borohydride, in a solvent such as methanol, dimethyl formamide or the mixture of one of these solvents with water, the compound of formula (I), in which $RR_1 = 0$.

In the case where R and AR' form a tetrahydronaphthyl ring and R_1 is hydrogen, the compounds corresponding to the formula (I) are prepared by causing the reaction of 4-hydroxy-2H-1-benzothiopyran-2-one with a compound of formula



in a solvent such as acetic acid in the presence of sulphuric acid and between 20°C and 150°C.

When $R_1 = OH$ or when R and AR' form a tetrahydronaphthyl ring and R_1 is hydrogen, the compounds are presented in the form of a mixture of diastereoisomers, as is demonstrated by thin-film chromatography or by high-pressure liquid chromatography.

The products of the invention have interesting properties, particularly as anticoagulants, such as shown by the results of tests carried out in connection with the wild rat (*Rattus Norvegicus*).

For this purpose, a bait with a dosage of 50 ppm of substance to be examined is prepared by impregnation of wheat smeared with vaseline with a mixture formed of starch and the product being investigated. This bait is then given for 3 days to adult male or female wild rats and the activity is examined by determining the mortality. The results obtained are indicated in Table 1 below.

Table 1

Activity on <i>Rattus Norvegicus</i> (Coumafene-sensitive strain)			
Compound	Dose	Duration of treatment	Mortality
1	50 ppm	3 days	10/10
2	50 ppm	3 days	10/10

Table I (continued)

Compound	Dose	Duration of treatment	Mortality
3	50 ppm	3 days	10/10
4	50 ppm	3 days	10/10
5	50 ppm	3 days	10/10
6	50 ppm	3 days	10/10
7	50 ppm	3 days	10/10
8	50 ppm	3 days	10/10

Coumafene = Warfarin = 4-hydroxy-3(1-phenyl-3-oxobutyl)-2H-1 benzopyran-2-one .

The compounds have also shown that, in the case of a single dose, they lead to a mortality of 100% of *Rattus Norvegicus*, as is indicated in the following Table II.

Table II

Activity on <i>Rattus Norvegicus</i> (Coumafene-sensitive strain)			
Compound	Dose	Duration	Mortality
1	50 ppm	1 day	10/10
2	50 ppm	1 day	10/10
3	50 ppm	1 day	10/10

On the other hand, it has been established that the thiopyrannic derivatives (I) of the invention are superior to the corresponding pyrannic derivatives, a result presenting an unexpected character. It is in fact known that the derivatives of the 4-hydroxycoumarine substituted in the 3 position have anti-vitamin K powers and are used as rodenticides. The works of Mentzer. Bull.Soc.Chim.Biol.25. pages 379-383 (1943), on the other hand, have shown that the replacement of the heterocyclic oxygen of the dicoumarol by sulphur resulted in a product of very low activity. The result has been confirmed and, on the other hand, this has been verified by the coumafene and its sulphur homologue, the thiocoumafene. These results are regrouped in the following Table III.

Table III

Activity on <i>Rattus Norvegicus</i> (coumafene-sensitive strain)			
Compound	Dose	Duration	Mortality
Coumafene	250 ppm	3 days	8/10
Thiocoumafene	250 ppm	3 days	5/10

The compound preferred according to Example 1, compared

with its oxygenated equivalent (A), the 3-[3(4'-bromo-4-biphenyl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxy-2H-[1]-benzopyran-2-one has an activity clearly superior than the same. The comparative tests were carried out on: *Rattus rattus* (coumafene-resistant strain); *Mus musculus* (coumafene-sensitive strain); and *Mus musculus* (coumafene-resistant strain):

The results obtained are indicated in the three following tables:

Table IV

Test on <i>Rattus rattus</i> (coumafene-resistant strain)			
Compound	Dose	Administration period	Mortality
1	5 ppm	2 days	20/20
A	5 ppm	2 days	11/20

Table V

Test on <i>Mus musculus</i> (coumafene-sensitive strain)			
Compound	Dose	Administration period	Mortality
1	5 ppm	7 days	20/20
A	5 ppm	7 days	15/20

Table VI

Test on <i>Mus musculus</i> (coumafene-resistant strain)			
Compound	Dose	Administration period	Mortality
1	5 ppm	7 days	10/10
A	5 ppm	7 days	7/10

The reading of these tables indicates that, in the case of the compounds conforming to the formula (I), the presence of the benzothiopyrannic ring leads to a better activity as compared with the benzopyrannic analogues.

Another unexpected effect which is obtained is the lower toxicity of the compounds of the invention as compared with their oxygenated homologues, especially on the non-rodent species. By way of example, the following test was carried out on the Beagle breed dog.:

3 dogs of Beagle breed received 50µg/kg of the compound according to Example 1, called compound 1, each day perorally. and 3 dogs of Beagle breed received the same dose of the compound A on the same basis. The biological supervision comprised the determination of the Quick time with stoppage of the test when

-5-

this latter reached 300 seconds. The curves of Figure 1 of the accompanying drawing show the effects obtained on the extension of the Quick time in the case of the Beagle dog; the Quick times in seconds are plotted as ordinates (TQs) and the treatment period in days (j) as abscissae. The curves 1, 2 and 3 correspond to the effects of the compound A and the curves 4, 5 and 6 to those of the compound 1. The letter M indicates the moment of death of an animal.

Moreover, it was observed that, in the case of the dogs treated with the compound A, the death occurred very quickly, with the increase of the Quick time, making impossible the application of an antidotal therapeutic. On the contrary, for the compound 1 of the invention, the lengthening of the Quick time and the deterioration of the clinical state are progressive. When the Quick time reaches 300 seconds, time is available for carrying out the application of a conventional safety treatment based on vitamin K₁; an I.V. injection of 5 mg/kg replaced by peroral treatment. In this way, the three dogs quickly show a return of the Quick time towards normal values, and this is definitive.

The compounds of the invention, and particularly the compound of the example constitute active anticoagulating substances of rodenticidal compositions, in association with a support which can be consumed by the rodents.

Given below are examples which illustrate the invention in non-limiting manner.

Example 1: 3-(3-(4'-bromo-4-biphenyl)-1,2,3,4-tetrahydro-1-naphthyl)-4-hydroxy-2H-1-benzothiopyran-2-one. C₃₁H₂₃BrO₂S

(formula 1). M.W. = 539.47

A solution of 14.2 g (0.08 mol) of 4-hydroxy-2H-1-benzothiopyran-2-one and 30.2 g (0.08 mol) of 3-(4'-bromo-4-biphenyl)-1,2,3,4-tetrahydro-1-naphthol in 60 ml of acetic acid is brought to 110°C. 2.6 ml of concentrated sulphuric acid are then added and the heating is continued for three hours. After having cooled, the reaction medium is poured into water and extracted with ether. The ethereal solution is washed with dilute soda and the formed insoluble oil is decanted and taken up in 10N hydrochloric acid. After extraction with ethyl acetate, evaporation and passage of the oil which is obtained on a silica

-6-

column eluted with chloroform, the obtained solid is recrystallised from toluene. There are obtained 9.5 g (yield 22%) of a white solid. $\gamma C = 0 : 1600 - 1620 \text{ cm}^{-1}$.

Gravimetric analysis:	C%	H%	Br%	S%	O%
Calculated:	69.01	4.30	14.81	5.94	5.93
Found:	68.97	4.15	14.85	5.82	

An examination by thin film chromatography indicates the presence in variable proportion of two isomers; one being in the majority. The result thereof, at the melting point level, is a region or band which, in the case of the product described, is $MP_G : 203 - 227^\circ C$. By purification, it is possible to separate the two isomers. The isomer in majority, recrystallised from toluene, melts at $227 - 230^\circ C$. The minority isomer melts at $209 - 211^\circ C$.

Example 2: 3-[3-(4'-bromophenoxy-4-phenyl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxy-2H-[1]-benzothiopyran-2-one. $C_{31}H_{23}BrO_3S$ (formula 2) - M.W. = 555.47.

Prepared according to Example 1 from 6 g (0.015 mol) of 3-[4'-bromophenoxy)-4-phenyl]-1,2,3,4-tetrahydro-1-naphthol and 2.7 g (0.015 mol) of 4-hydroxy-2H-1-benzothiopyran-2-one. After treatment with hexane, there is obtained a beige solid $MP_G : 95 - 105^\circ C$. IR $\gamma C = 0 : 1595$.

Gravimetric analysis	C%	H%	Br%	O%	S%
Calculated:	67.03	4.17	14.39	8.64	5.77
Found:	67.22	4.23	14.09		5.79

Example 3 3-[3-(4'-chloro-4-biphenyl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxy-2H-[1]-benzothiopyran-2-one (formula 3) $C_{31}H_{23}ClO_3S$. M.W. 495.01

Prepared according to Example 1 from 7 g (0.04 mol) of 4-hydroxy-2H-1-benzothiopyran-2-one and 13.4 g (0.04 mol) of 3-(4'-chloro-4-biphenyl)-1,2,3,4-tetrahydro-1-naphthol. After purification in ethyl acetate, there is obtained a whitish solid $MP_G : 220 - 2^\circ C$, IR $\gamma C = 0 : 1590$

Gravimetric analysis	C%	H%	Cl%	O%	S%
Calculated:	75.21	4.68	7.16	6.46	6.48
Found:	75.19	4.72	7.02		6.20

Example 4 3-[3-(4'-bromo-4-biphenyl)-3-oxo-1-phenyl]-3-propyl-4-hydroxy-2H-[1]-benzothiopyran-2-one (formula 4) $C_{30}H_{21}BrO_3S$. M.W. 541.45.

5 g (0.020 mol) of 4-hydroxy-2H-1-benzothiopyran-2-one and 9.1 g (0.025 mol) of 3-(4'-bromo-4-biphenyl)-1-phenyl-3-propenone are

-7-

placed in 50 ml of ethanol containing 0.4 ml of piperidine. This suspension is placed under reflux and the quantity of dioxane necessary for obtaining a solution is added. The medium is then maintained under reflux for 6 hours. After cooling to ambient temperature, the insoluble substance is hydroextracted and the filtrate is strongly cooled. The formed precipitate is hydroextracted and purified by passage over a silica column and then recrystallised from toluene. A clear beige solid is thereby obtained. MP_g : 169-171°C. $IR_{\gamma C} = 0 : 1580$.

<u>Gravimetric analysis:</u>	C%	H%	Br%	O%	S%
Calculated	66.54	3.91	14.76	8.87	5.92
Found	66.43	3.82	14.73		5.80

Example 5: 3-(4'-bromo-4-biphenyl)-3-hydroxy-1-phenyl-3-propyl-4-hydroxy-2H-17-benzothiopyran-2-one (formula 5) $C_{30}H_{23}BrO_3S$.
M.W. = 543.46.

Placed in a 250 ml reactor are 7.9 g (0.0146 mol) of the product of Example 4, 70 ml of ethanol; 1.7 g (0.043 mol) of soda in pellet form. The whole is then brought to 30°C and there are added, in small fractions, 1.1 g (0.0292 mol) of sodium borohydride. The product is then left for 2 hours at 30-35°C, filtered and the filtrate is poured on to the concentrated H_2O-HCl mixture (600 ml - 30 ml). The formed white precipitate is drained and this is purified by passage on a silica column, being eluted with the cyclohexane- $CHCl_3$ -MeOH mixture: 125 - 75 -25.

MP_g : 110-120°C, $IR_{\gamma C} = 0 : 1600$.

<u>Gravimetric analysis:</u>	C%	H%	Br%	O%	S%
Calculated:	66.30	4.27	14.71	8.83	5.90
Found:	66.25	4.28	14.82		5.86

Example 6: 3-(4'-chloro-4-biphenyl)-3-oxo-1-phenyl-3-propyl-4-hydroxy-2H-17-benzothiopyran-2-one (formula 6)

$C_{30}H_{21}ClO_3S$. M.W. = 496.99.

Prepared according to Example 4 from 8.7 g (0.0273 mol) of 3-(4'-chloro-4-biphenyl)-1-phenyl-3-propenone and 5.3 (0.03 mol) of 4-hydroxy-2H-17-benzothiopyran-2-one. After purification in toluene, a white solid is obtained. MW_g 171-3°C.

$IR_{\gamma C} = 0 : 1590$.

<u>Gravimetric analysis:</u>	C%	H%	Cl%	O%	S%
Calculated	72.50	4.26	7.13	9.66	6.45
Found	72.76	4.37	7.25		6.21

-8-

Example 7: 3-(4'-chloro-4-biphenyl)-3-hydroxy-1-phenyl-3-propenyl-4-hydroxy-2H-17-benzothiopyran-2-one (formula 7)

$C_{30}H_{23}ClO_3S$. M.W. = 499.

Prepared according to Example 5 from 8 g (0.0161 mol) of the product of Example 6. 1.9 g (0.0474 mol) of soda in pellet form, 50 ml of dimethyl formamide, 10 ml of water and 1.2 g (0.0322 mol) of sodium borohydride. A beige product is isolated.

MP_G : 105-125°C (decomposition). IR_γC = 0 : 1585

<u>Gravimetric analysis:</u>	C%	H%	Cl%	S%	O%
Calculated	72.20	4.65	7.11	6.42	9.62
Found	72.24	5.01	7.17	6.21	

Example 8 : 3-(4'-bromo-4-biphenyl)-3-oxo-1-(2-thienyl)-3-propenyl-4-hydroxy-2H-17-benzothiopyran-2-one (formula 8).

$C_{28}H_{19}BrO_3S_2$. M.W. = 547.47

Prepared according to Example 4 from 11 g (0.03 mol) of 3-(4'-bromo-4-biphenyl)-1(2-thienyl)-3-propenone and 5.8 g (0.033 mol) of 4-hydroxy-2H-17-benzothiopyran-2-one.

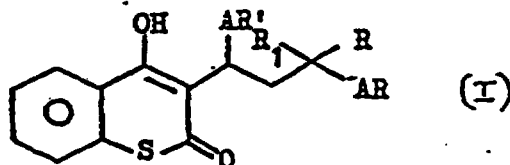
Thereby obtained by recrystallisation from acetic acid is a white solid. MP_G: 140-5°C.

IR_γC=O : 1600.

<u>Gravimetric analysis:</u>	C%	H%	Br%	S%	O%
Calculated	61.42	3.50	14.60	11.71	8.77
Found	61.65	3.52		12.00	

Claims for the contracting states: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE.

1. 4-hydroxy-2H-1-benzothiopyran-2-ones, characterised by the formula:



in which, when R_1 is hydrogen, R and AR' may form a tetrahydronaphthyl ring; R and R_1 may form a carbonyl group with the adjacent carbon atom; when R_1 is hydrogen, R may be a hydroxyl group; AR is a biphenyl or phenoxyphenyl group, possibly substituted by a halogen; AR' is a phenyl or a thienyl group or may form with R a tetrahydronaphthyl ring when R_1 is hydrogen.

2. 3-[3-(4'-bromo-4-biphenyl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxy-2H-17-benzothiopyran-2-one, according to claim 1.

3. Process for preparing the compounds of claim 1, characterised in that it consists in causing reaction of the 4-hydroxy-2H-1-benzothiopyran-2-one with a compound of formula



-8-

Example 7: 3-(4'-chloro-4-biphenyl)-3-hydroxy-1-phenyl-3-propenyl-4-hydroxy-2H-17-benzothiopyran-2-one (formula 7)

$C_{30}H_{23}ClO_3S$. M.W. = 499.

Prepared according to Example 5 from 8 g (0.0161 mol) of the product of Example 6. 1.9 g (0.0474 mol) of soda in pellet form, 50 ml of dimethyl formamide, 10 ml of water and 1.2 g (0.0322 mol) of sodium borohydride. A beige product is isolated.

MP_G : 105-125°C (decomposition). IR_{γC} = 0 : 1585

Gravimetric analysis:	C%	H%	Cl%	S%	O%
Calculated	72.20	4.65	7.11	6.42	9.62
Found	72.24	5.01	7.17	6.21	

Example 8 : 3-(4'-bromo-4-biphenyl)-3-oxo-1-(2-thienyl)-3-propenyl-4-hydroxy-2H-17-benzothiopyran-2-one (formula 8).

$C_{28}H_{19}BrO_3S_2$. M.W. = 547.47

Prepared according to Example 4 from 11 g (0.03 mol) of 3-(4'-bromo-4-biphenyl)-1(2-thienyl)-3-propenone and 5.8 g (0.033 mol) of 4-hydroxy-2H-17-benzothiopyran-2-one.

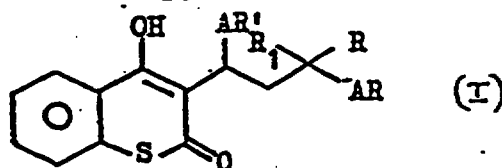
Thereby obtained by recrystallisation from acetic acid is a white solid. MP_G: 140-5°C.

IR_{γC}=0 : 1600.

Gravimetric analysis:	C%	H%	Br%	S%	O%
Calculated	61.42	3.50	14.60	11.71	8.77
Found	61.65	3.52		12.00	

Claims for the contracting states: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE.

1. 4-hydroxy-2H-1-benzothiopyran-2-ones, characterised by the formula:



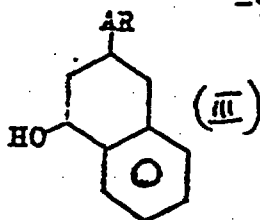
in which, when R_1 is hydrogen, R and AR' may form a tetrahydronaphthyl ring; R and R_1 may form a carbonyl group with the adjacent carbon atom; when R_1 is hydrogen, R may be a hydroxyl group; AR is a biphenyl or phenoxyphenyl group, possibly substituted by a halogen; AR' is a phenyl or a thienyl group or may form with R a tetrahydronaphthyl ring when R_1 is hydrogen.

2. 3-[3-(4'-bromo-4-biphenyl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxy-2H-17-benzothiopyran-2-one, according to claim 1.

3. Process for preparing the compounds of claim 1, characterised in that it consists in causing reaction of the 4-hydroxy-2H-1-benzothiopyran-2-one with a compound of formula



-9-

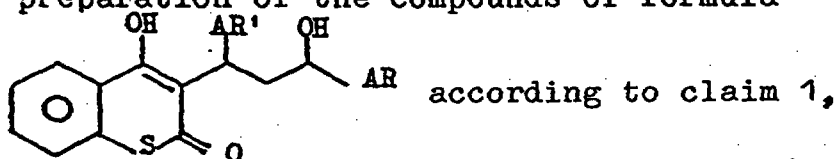


when AR' and R form a tetrahydronaphthyl ring; or with a compound of general formula

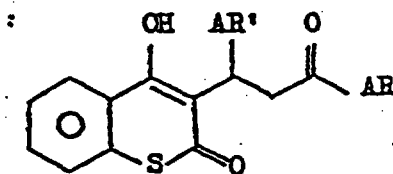


grouping, with the adjacent carbon atom.

4. Process for preparation of the compounds of formula



characterised in that these compounds are obtained by reduction of compounds of formula:



5. Rodenticide composition, characterised in that it contains, as active substance, a compound according to claim 1 in association with a support which can be consumed by the rodents.

6. Rodenticide composition according to claim 5, characterised in that it contains, as active substance, the 3-~~3~~⁴-bromo-4-biphenyl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxy-2H-[1]-benzothiopyran-2-one.