

PATENT SPECIFICATION

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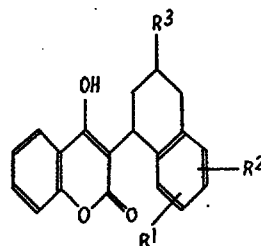
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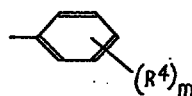
(54) ANTI COAGULANT 3-TETRAHYDRONAPHTHYL-4-HYDROXYCOUMARIN DERIVATIVES

(71) We, WARD BLENKINSOP AND COMPANY LIMITED, a British Company, of Fulton House, Empire Way, Wembley, Middlesex, 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 of general formula I having anti-coagulant properties which are useful as rodenticides or in human medicine.



Where R¹ and R² are the same or different and are hydrogen or halogen atoms preferably chlorine or bromine, or straight or branched chain alkyl or alkoxy groups preferably having up to 6 carbon atoms, R³ is an aryl group having the formula

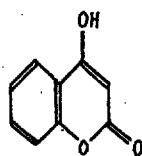


Where m is 1 or 2, and R⁴ is the same or different and is a halogen atom; a straight or branched chain alkyl or alkoxy group, preferably containing at least 2, more preferably from 5 to 12 carbon atoms; a cycloalkyl, preferably cyclohexyl group; an aralkyl, preferably α -aralkyl group; a phenyl or a phenoxy group, or a halogeno, preferably para halogeno, substituted derivative thereof. The halogen atom or atoms are preferably chlorine or bromine. Where m is 1, R⁴ is preferably in the para position and when m is 2 one of the R⁴ groups is preferably in the para position. Preferably R³ contains at least 1 but not more than 3 and optimally not more than 2 halogen atoms. Further, R³ is preferably an halogenophenyl group, a bi-phenyl group, an halogeno bi-phenyl group, a phenoxyphenyl group or an halogenophenoxyphenyl group, more preferably a 4-chlorophenyl group, a 4-bromophenyl group, a 4-(4'-chloro)biphenyl group, a 4-(4'-bromo)biphenyl group,

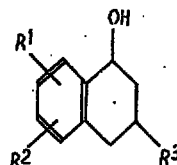
a 4-(4'-bromo)-phenoxyphenyl group or a 4-(4'-chloro)phenoxyphenyl group.

The invention also includes a rodenticidal composition comprising a compound of the invention in combination with a carrier and a method of killing rodents comprising feeding the rodents with an effective amount of the composition.

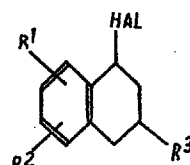
Compounds of the general formula I may be prepared by condensing 4-hydroxy coumarin (II) with compounds of general formula (III) without a solvent or in a solvent such as acetic acid in the presence of a dehydrating agent such as sulphuric acid or by condensing 4-hydroxy coumarin (II) with a compound of general formula IV with or without the use of a solvent.



II



III

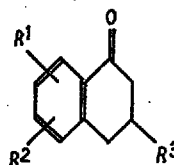


IV

R^1 , R^2 and R^3 have the meanings given previously and Hal is halogen preferably chlorine or bromine.

Compounds of structure IV may be prepared from compounds of general structure III by treatment with an halogenating agent such as phosphorus tribromide, phosphorus trichloride or thionyl chloride in an inert solvent such as methylene chloride, chloroform or carbon tetrachloride.

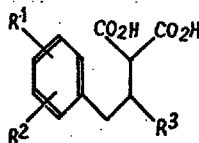
Compounds of general formula III may be prepared by reduction of compounds of general formula V in which R^1 , R^2 and R^3 have the meanings given previously, with for example hydrogen in the presence of a catalyst, sodium borohydride in a solvent such as methanol or ethanol, aluminium isopropoxide in isopropanol or by any other means commonly used for the reduction of ketones to alcohols.



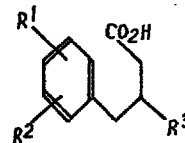
V

Compounds of general formula V may be prepared by treatment of compounds of general formula VI or VII with a condensing agent such as polyphosphoric acid.

In the case of cyclisation of compounds of general formula VI an elevated temperature is necessary so that decarboxylation occurs.



VI



VII

in which R^1 , R^2 and R^3 have the meanings previously given.

Compounds of general formula VI or VII may be prepared by treating a salt of malonic ester derivative, such as the sodium salt of diethyl malonate, in a solvent such as methanol or ethanol or dimethyl formamide with a compound of general formula VIII in which R^1 , R^2 , R^3 and Hal have the meanings given previously, followed by hydrolysis with for example sodium or potassium hydroxide in aqueous ethanol or hydrochloric or sulphuric acid. Compounds of general formula VII may be prepared from compounds of general formula VI by heating at or near the melting point to effect decarboxylation.

Compounds of general formula VI or VII may also be prepared from compounds of general formula VIII by other methods commonly used for the

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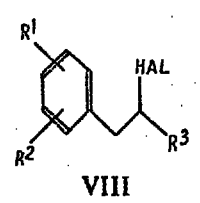
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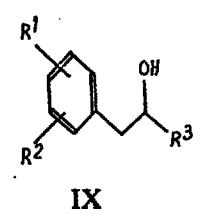
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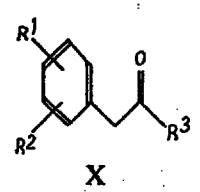
conversion of Hal in formula VIII into a $\text{CH}_2\text{CO}_2\text{H}$ or $\text{CH}(\text{CO}_2\text{H})_2$ group or from compounds of general formula X by methods commonly used for the conversion of ketones into acetic acid derivatives with the addition of two carbon atoms.



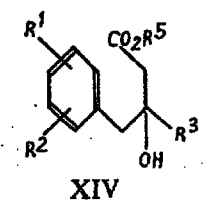
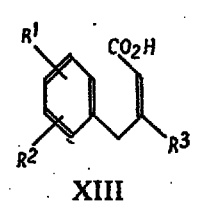
Compounds of general formula VIII may be prepared by treatment of compounds of general formula IX in which R^1 , R^2 and R^3 have the meanings given previously, with for example phosphorus tribromide, phosphorus trichloride or thionyl chloride in an inert solvent such as methylene chloride, chloroform or carbon tetrachloride.



Compounds of general formula IX may be prepared by the reduction of compounds of general formula X in which R^1 , R^2 and R^3 have the meanings given previously, with, for example, sodium borohydride in a solvent such as ethanol or methanol, aluminium isopropoxide in isopropanol (a Meerwein Ponndorf reduction), hydrogen in the presence of a catalyst or by such other methods as are commonly used for the reduction of ketones to alcohols.



Compounds of the general formula VII may also be prepared by the reduction of compounds of the general formula XIII in which R^1 , R^2 , R^3 have the meanings previously given. The reduction may conveniently be effected by catalytic hydrogenation, e.g. by gaseous H_2 over platinum oxide catalyst in solution in acetic acid. Other well known techniques of reduction of a double bond may also be employed as appropriate.



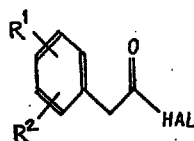
Compounds of the general formula XIII may be prepared from compounds of the general formula XIV, in which R^1 , R^2 , and R^3 have the meanings given previously and R^3 represents a hydrogen atom or the residue of an ester-forming alcohol, by dehydration and when the starting material is in the ester form hydrolysis of the ester.

Conveniently this can be done by treating compounds of the general formula XIV with toluene sulphonic acid in toluene to dehydrate, e.g. under a Dean-Stark apparatus, and then if necessary hydrolysing the ester in aqueous, ethanolic alkali.

(e.g. NaOH) and distilling off the ethanol.

Compounds of the general formula XIV may be prepared by treating compounds of the general formula X in solution with zinc and an halogeno acetic acid ester, e.g. ethyl bromoacetate. A suitable solvent is benzene and the reaction is conveniently carried out at elevated temperature, e.g. under reflux. The product at this point is in the ester form and, if desired, the acid form may conveniently be made by addition of dilute mineral acid to hydrolyse the ester and isolation of the acid form of the compound of the general formula XIV from the benzene layer. Compounds of the general formula XIV may also be prepared from compounds of the general formula X by other methods commonly used for the conversion of ketones to β -hydroxy acetic acid derivatives with the addition of two carbon atoms.

Compounds of general formula X may be prepared by the Friedel-Crafts condensation of a compound of general formula XI in which R^1 , R^2 , and Hal have the meanings given previously, with a compound of general formula XII in which R^3 has the meaning given previously, in the presence of a Lewis Acid such as aluminium chloride in an inert solvent such as methylene chloride or carbon disulphide.



XI



XII

The synthetic routes described above are illustrated in the outline reaction sequence shown in the accompanying drawings.

The compounds with which this invention is concerned can exist as both cis and trans isomers. Compounds obtained by the methods described above show two spots on t.l.c., and we surmise that they are produced as a mixture of the cis and trans isomers. We have now separated the two isomers (see Examples 1 and 8) but we have not yet identified which is cis and which is trans. Further the compounds of the invention used in the trials described below were not entirely pure and so the results given may differ somewhat from those achieved with pure materials.

The position of the substituents R^1 and R^2 in the phenyl ring of the tetrahydronaphthalene group is not believed to be critical with respect to the anticoagulant activity of the products. However, clearly, using the synthetic route described, some of the substituted phenylacetic acids used as starting materials will produce intermediate tetralones in more than one isomeric form. This is a disadvantage from the point of view of the synthesis of pure compounds but it is believed that it would be possible to use final products made from mixtures of such isomers as anticoagulants. Among mono-substituted phenylacetic acids (i.e. when either R^1 or R^2 but not both is hydrogen) ortho- and para-forms produce only one tetralone whereas meta-forms produce two the 6-, and the 8-substituted. Among di-substituted phenyl acetic acids the 2, 3-, 2,4- and 2,5- forms produce only one corresponding tetralone whereas the 3,4- 3,5- and 4,5- forms can produce corresponding pairs of isomers. Mixed tetralone intermediates will, of course, produce mixed tetrahydro-naphthalene systems in the final products. From a practical point of view para-substituted phenylacetic acids are the most readily available commercially, ortho-forms are rather less readily available and meta-forms rather difficult to obtain. Thus para-substituted and 2,4-disubstituted phenylacetic acids are preferred, because of their more ready availability, in the process of the present invention. The following Examples illustrate preparation of compounds according to the invention. All temperatures are in degrees Centigrade.

EXAMPLE 1.

3-(3-*p*-Biphenyl-1,2,3,4-tetrahydronaphth-1-yl-4-hydroxy coumarin

A. α -Benzyl-*p*-phenylbenzyl alcohol

(i) Sodium borohydride (6.7 g) was added to a suspension of benzyl-*p*-biphenyl ketone (47.4 g) in ethanol (150 ml). The solution was heated to boiling, the heat removed and the solution stirred for one hour. The mixture was diluted with water

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treating o ad reaction product iently be on of ne layer ounds of carbon	5	5	and extracted with chloroform. The chloroform was evaporated and the residue collected with petroleum ether (b.p. 40—60°) to give 46.7 g of α -benzyl- <i>p</i> -phenyl benzyl alcohol; m.p. 107—108°. (Found: C, 87.7; H, 6.3 $C_{28}H_{18}O$ requires: C, 87.6; H, 6.6%)	5
	10	10	(ii) Benzyl <i>p</i> -biphenyl ketone (41.6 g) aluminium isopropoxide (40 g) and isopropanol (200 ml) were heated to boiling and the acetone/isopropanol distilled out (120 ml of distillate was collected in four hours). The mixture was cooled, decomposed by the addition of hydrochloric acid plus water and extracted with methylene chloride. The methylene chloride was washed (H_2O), dried ($MgSO_4$) and evaporated to give 39.9 g of α -benzyl- <i>p</i> -phenylbenzyl alcohol; m.p. 105—107°.	10
el-Crafts Hal have in which such as carbon	15	15	B. α -Benzyl- <i>p</i> -phenylbenzyl bromide and α -Benzyl- <i>p</i> -phenyl benzyl chloride (i) Phosphorus tribromide (7 ml) was added dropwise with stirring to a solution of α -Benzyl- <i>p</i> -phenyl benzyl alcohol (41.7 g) in methylene chloride (150 ml). After three hours the mixture was added to water, the methylene chloride separated off, washed (H_2O) and evaporated. The residue was recrystallized from petroleum ether (b.p. 80—100°) to give 46.1 g of α -benzyl- <i>p</i> -phenylbenzyl bromide; m.p. 99—100°. (Found: C, 71.6; H, 5.35 $C_{20}H_{17}Br$ required: C, 71.2; H, 5.1%)	15
	20	20	(ii) Similarly using thionyl chloride (2.9 ml) α -benzyl- <i>p</i> -phenyl benzyl alcohol (10 g) and methylene chloride (50 ml) there was obtained after recrystallizing from petroleum ether (b.p. 60—80°) 9.5 g of α -benzyl- <i>p</i> -phenylbenzyl chloride; m.p. 89—93°. (Found: C, 82.0; H, 5.9 $C_{20}H_{17}Cl$ requires C, 82.0; H, 5.8%)	20
reaction	20	25	C. (1- <i>p</i> -Biphenyl-2-phenylethyl) malonic acid (i) α -Benzyl- <i>p</i> -phenyl benzyl bromide (16.8 g) was added to a solution of the sodium salt of diethyl malonate (prepared from 7.7 ml of diethyl malonate and 2.0 g of 60% sodium hydride) in dimethylformamide (40 ml). The solution was stirred and heated at 97° for sixteen hours, cooled and then diluted with methylene chloride and water. The mixture was filtered and the methylene chloride washed (H_2O) and evaporated. Sodium hydroxide (15 g) water (100 ml) and ethanol (100 ml) were added to the residue and the mixture heated on a steam bath for three hours the ethanol being distilled off. The solution was filtered and the insoluble material washed with water. The filtrate was acidified and extracted with ethyl acetate. The ethyl acetate was evaporated and the residue collected with petroleum ether (b.p. 40—60°) to give 11.4 g of 1- <i>p</i> -biphenyl-2-phenylethyl malonic acid; m.p. 186—189° dec. A sample recrystallized from ethyl acetate had a m.p. 199—201 dec. (Found: C, 76.4; H, 5.4 $C_{23}H_{20}O_4$ requires C, 76.65; H, 5.6%)	25
both cis ove show of the cis s 1 and 8) rther the t entirely with pure	25	30	(ii) In a similar manner using α -benzyl- <i>p</i> -phenylbenzyl chloride (9.0 g) 60% sodium hydride (1.31 g), diethyl malonate (5 ml) and dimethyl formamide (26 ml) was obtained 2.1 g of 1- <i>p</i> -diphenyl-2-phenylethyl malonic acid; m.p. 190—195° dec.	30
he tetra- t to the etic route materials This is a s but it is es of such i.e. when only one l. Among only one duce cor- f course, From a st readily nd meta- bstituted ity, in the aration of degrees	30	35	D. 3- <i>p</i> -Biphenyl tetralin-1-one (i) (1- <i>p</i> -Biphenyl-2-phenylethyl) malonic acid (93.5 g) and polyphosphoric acid (500 g) were heated to 160° for one hour. Ice and methylene chloride were added to the mixture which was stirred until dissolved. The methylene chloride was separated off, passed through an alumina column which was eluted with methylene chloride. The methylene chloride was evaporated and the residue collected with petroleum ether to give 61.8 g of 3- <i>p</i> -biphenyl tetralin-1-one; m.p. 75—77°. A sample recrystallised from petroleum ether (b.p. 80—100) had a m.p. 92—94°. (Found: C, 88.3; H, 6.3 $C_{22}H_{18}O$ requires: C, 88.6; H, 6.1%)	35
	40	45	(ii) (1- <i>p</i> -Biphenyl-2-phenylethyl) malonic acid (10.0 g) was melted (temperature 200°). After cooling the residue was dissolved in water (300 ml) plus ammonia (30 ml) at 90°. The solution was filtered, acidified and extracted three times with chloroform. The chloroform was evaporated and the residue collected with petroleum ether (b.p. 40—60) to give 3- <i>p</i> -biphenyl-4-phenylbutyric acid (8.7 g) m.p. 175—178°. A sample recrystallised from ethanol had a m.p. 177—179°. (Found: C, 82.9; H, 6.2 $C_{22}H_{20}O_2$ requires: C, 83.5; H, 6.4%)	45
	45	50	3- <i>p</i> -biphenyl-4-phenylbutyric acid (7.7 g) and polyphosphoric acid (35 g) were heated for 30 minutes at 160° and 30 minutes at 190° and the reaction mixture worked up as described in (i) to give on recrystallising from petroleum ether (b.p. 80—100°) 4.3 g 3- <i>p</i> -biphenyl tetralin-1-one; m.p. 92—94°.	50
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-biphenyl , the heat with water	55			

E. 3-*p*-Biphenyl tetralin-1-ol

(i) Sodium borohydride (8.4 g) was added portionwise with stirring over 15 mins to a suspension of 3-*p*-biphenyl tetralin-1-one (65.8 g) in ethanol (200 ml). The mixture was heated to 60° stirred for 30 minutes and diluted with water. The mixture was extracted three times with chloroform, and the chloroform washed (H₂O), evaporated and the residue collected with petroleum ether (b.p. 40–60°) to give 62.4 g 3-*p*-biphenyl tetralin-1-ol; m.p. 145–150°.

A sample purified by chromatography on silica using methylene chloride as an eluent and then recrystallising from ethanol had a m.p. 159°.
(Found: C, 87.7; H, 7.0 C₂₂H₂₀O requires: C, 88.0; H, 6.7%)

(ii) 3-*p*-Biphenyl tetralin-1-one (13.5 g) isopropanol (60 ml) and aluminium isopropoxide (12 g) were heated to boiling and the acetone/isopropanol distilled out (31 ml of distillate was collected over one hour). After cooling hydrochloric acid (14 ml) plus water (57 ml) was added and the solid filtered off and washed with water to give 11.3 g of 3-*p*-biphenyl tetralin-1-ol; m.p. 131–139°.

A sample purified by chromatography on silica using methylene chloride as an eluant and then recrystallising from ethanol had a m.p. 145°.

The products obtained above may be isomeric or mixtures of isomers (cis and trans) but either product may be used in the subsequent reaction with 4-hydroxycoumarin.

F. 3-(3-*p*-Biphenyl-1,2,3,4-tetrahydronaphth-1-yl)-4-hydroxy coumarin

(i) Sulphuric acid (0.5 ml; 60°Be) was added to a mixture of 4-hydroxy coumarin (4.8 g), 3-*p*-Biphenyl tetralin-1-ol (9.0 gms; obtained by sodium borohydride reduction) and acetic acid (15 ml) at 110°. The mixture was stirred and heated at 110° for one hour, then diluted with water and extracted twice with ether. The ether was extracted three times with dilute sodium hydroxide solution and the combined alkaline extracts acidified and extracted three times with chloroform. The chloroform was evaporated to a small volume and applied to a silica column which was eluted with chloroform. The fractions containing two components having R_f values of 0.45 and 0.55 were evaporated and the residue crystallised from ethyl acetate to give 3.75 g. of 3-(3-*p*-biphenyl-1,2,3,4-tetrahydronaphth-1-yl)-4-hydroxy coumarin; m.p. 210–215°. Recrystallisation gave material of m.p. 215–217°.

(Found: C, 83.5; H, 5.4 C₃₁H₂₄O₃ requires: C, 83.8; H, 5.4%)

(ii) 4-Hydroxycoumarin (1.6 g) and 3-*p*-biphenyltetralin-1-ol (3 g; obtained by sodium borohydride reduction) were heated at 160° for one hour. The mixture was extracted with ether and then worked up as described in (i) to give 0.9 of 3-(3-*p*-biphenyl-1,2,3,4-tetrahydronaphth-1-yl)-4 hydroxy coumarin; m.p. 211–212°.

(iii) Phosphorus tribromide (0.7 ml) was added dropwise with stirring to a suspension of 3-*p*-biphenyltetralin-1-ol (m.p. 159°; 6.0 g, prepared by sodium borohydride reduction) in methylene chloride (50 ml) the temperature being kept below 0°. After stirring for one hour the mixture was washed (H₂O) dried (MgSO₄) evaporated and the residue chromatographed on silica using benzene. The benzene was evaporated and the residue recrystallised from petroleum ether (b.p. 80–100°) to give 1-bromo-3-*p*-biphenyltetralin (5.0 g; 70%) m.p. 132° dec.

1-Bromo-3-*p*-biphenyltetralin (3.6 g) and 4-hydroxycoumarin (1.6 g) were heated at 130–135° for thirty minutes. The residue was stirred with benzene (25 ml) the insoluble material filtered off and filtrate evaporated to give a solid which was collected with petroleum ether (b.p. 60–80°) to give 3.5 g of 3-(3-*p*-biphenyl-1,2,3,4-tetrahydronaphth-1-yl)-4-hydroxy coumarin; m.p. 202–208°.

(iv) 4-Hydroxycoumarin (14.4 g) 3-*p*-biphenyltetralin-1-ol (27.0 g; prepared by aluminium isopropoxide reduction) and acetic acid (45 ml) were heated to 105° and 80% sulphuric acid (1.5 ml) added over 3 minutes with stirring. After stirring at 110° for one hour, water (100 ml) was added and the mixture extracted with chloroform (100 ml) some insoluble material being rejected. The chloroform solution was chromatographed through alumina which was eluted with chloroform and the chloroform evaporated. The residue was extracted with hot hexane (150 ml) and the insoluble residue dissolved in hot toluene (any insoluble material being rejected) and hexane (200 ml) added to give 13.2 g of 3-(3-*p*-biphenyl-1,2,3,4-tetrahydronaphth-1-yl)-4-hydroxy coumarin; m.p. 213–216°.

The products obtained in Example 1 F (i) (ii) (iii) and (iv) are mixtures of two isomers as indicated by t.l.c. having R_f values of 0.18 and 0.24 (benzene/silica). These isomers may be separated by preparative t.l.c. on silica the plates being run

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several times with benzene, or by column chromatography on silica using benzene as an eluant.

The slower running isomer was obtained by crystallising from ethyl acetate m.p. 227—229°. The faster-running isomer was obtained by crystallising from ethyl acetate m.p. 200—202°.

The products obtained in Example 1 F (i) (ii) and (iv) contain the two isomers in approximately equal proportions, whereas the product obtained in Example 1 F (iii) contains the slow-running isomer and the fast-running isomer in the approximate ratio of 5:1.

EXAMPLE 2.

An alternative method to that described in Example 1 may be used for conversion of benzyl *p*-diphenyl ketone into 3-*p*-biphenyl-4-phenyl butyric acid:

A. Ethyl-3-*p*-biphenyl-3-hydroxy-4-phenyl butyrate

Benzyl *p*-biphenyl ketone (10 g), zinc dust (3.7 g) and benzene were stirred and heated at 80° and ethyl bromoacetate (8.6 g) in benzene (20 ml) added dropwise. After stirring and heating 3 hours the mixture was left sixteen hours and then decomposed by the addition of 2N sulphuric acid (100 ml). The benzene was separated, washed (NaHCO₃) and evaporated to give a residue which was recrystallised from petroleum ether to give 11.2 g of ethyl-3-*p*-biphenyl-3-hydroxy-4-phenyl butyrate; m.p. 95—97°.
(Found: C, 80.1; H, 6.7 C₂₄H₂₄O₃ requires: C, 80.0; H, 6.7%)

B. 3-Benzyl-3-*p*-biphenylacrylic acid

Ethyl 3-*p*-biphenyl-3-hydroxy-4-phenylbutyrate (5 g) toluene sulphonic acid (0.1 g) and toluene (100 ml) were heated under reflux 3 hours water being removed using a Dean-Stark apparatus. The solution was evaporated, sodium hydroxide (3.0 g), water (30 ml) and ethanol (30 ml) added to the residue and the mixture heated on a steam bath for two hours, the ethanol being distilled off. Water (100 ml) was added and the solution extracted with ether. The aqueous layer was acidified, extracted twice with ethyl acetate and the ethyl acetate dried (MgSO₄) and evaporated. The residue was collected with petroleum ether (b.p. 40—60°) to give 4.24 g of 3-benzyl-3-*p*-biphenyl acrylic acid; m.p. 165—174°. A sample recrystallised from toluene had a m.p. 170—178°.

3-*p*-Biphenyl-4-phenylbutyric acid

3-Benzyl-3-*p*-biphenyl acrylic acid (5.0 g), acetic acid (100 ml) and platinum oxide (0.3 g) were shaken in an atmosphere of hydrogen at NTP for 4 hours. The solution was filtered and evaporated and the residue recrystallised from ethanol to give 2.2 g of 3-*p*-biphenyl-4-phenylbutyric acid; m.p. 172—173°.

The following table (Table I) gives details of compounds prepared by the synthetic routes described in Examples 1 and 2.

TABLE 1

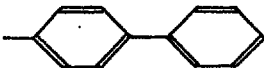
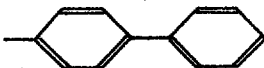
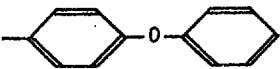
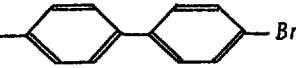
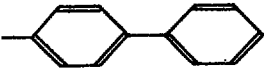
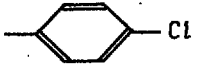
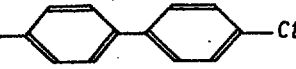
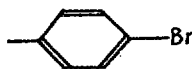
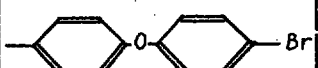
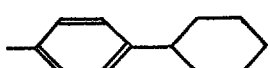
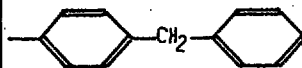
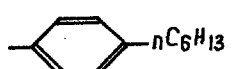
Example No.	SUBSTITUENTS			m.p.t. °C	ANALYSIS			
					Experimental		Theoretical	
	R ¹	R ²	R ³		C	H	C	H
1 i	H	H		215-217	83.5	5.4	83.8	5.4
ii				211-212				
iii				202-208				
iv				213-216				
3	Cl(7)	H		255-256	77.4	4.75	77.3	4.8
4	H	H		200-201	80.45	5.2	80.85	5.25
5	H	H		228-230	71.1	4.4	71.2	4.4
6	Me(7)	H		230-232	83.7	5.8	83.8	5.7
7	H	H		115-130	74.3	5.2	74.5	5.2
8 i.	H	H		222-225	77.5	5.0	77.8	4.8
ii				228-230	77.5	5.0		
iii				235-237	77.6	5.1		
iv				233-234	77.8	4.9		

TABLE 1 (continued)

S	eoretical
8	5.4
3	4.8
85	5.25
2	4.4
8	5.7
5	5.2
8	4.8

Example No.	SUBSTITUENTS			m.p.t. °C	ANALYSIS			
	R ¹	R ²	R ³		Experimental		Theoretical	
					C	H	C	H
9	H	H		210–213	67.3	4.2	67.2	4.3
10	H	H		199–201	69.1	4.0	69.1	4.3
11	H	H		170–174	82.9	6.8	82.6	6.7
12	H	H		75–85	83.6	5.9	83.8	5.7
13	H	H		109–111	82.4	7.1	82.3	7.1

Examples 3, 4, 5, 6, 7, 8, 10, 11, 12, 13 were made by the route described in Example 1F (ii) Examples 9 and 13 were made by the route described in Example 1F (iii).

In Example 8 the product from the direct condensation of 3-(4'-Chloro-4-biphenyl) tetralin-1-ol and 4-hydroxycoumarin was chromatographed on silica using chloroform as eluant and the fractions containing components having R_f values 0.8 and 0.71 collected and evaporated. The residue was rechromatographed on silica using chloroform/trichloroethylene (1:1) as eluant to give four fractions. The first fraction, (i), contained the component having an R_f value of 0.8, the next two fractions, (ii) and (iii), contained both components and the fourth fraction, (iv), contained the component having an R_f value of 0.71. The fractions were evaporated and the residue recrystallised from ethyl acetate to give the properties listed in the table.

Pharmacological Properties

The products of the invention have very high levels of anti-coagulant activity relative to that of commercially available compounds. More important is the activity of the materials against an anti-coagulant resistant strain of rats. The ratio of activity resistant:non-resistant is far smaller than that seen in other compounds, i.e. there is little resistance to the compounds of the invention.

We believe that the increased activity of the compounds of the invention to resistant rats is due to a high level of affinity between the particular stereo-

chemical configuration of these materials and the receptor site of the modified resistant enzyme.

RESULTS OF TRIALS

The results shown below were obtained by the following methods:

5 1. *Prothrombins*: Male rats were used throughout. The anti-coagulants were injected by the intraperitoneal route at the same time on three consecutive days. The solvent used was polyethylene glycol 300.

10 F.F.G.M. laboratory pellets (compounded rat food used in animal houses) and tap water were available throughout the treatment period.

Prothrombin times were determined 24 hours after the last injection by the one stage method of Quick.

15 E.D. 50s were estimated by calculating the percentage extension of prothrombin time, plotting results upon logarithmic probability sheets and drawing the best line of fit. The E.D.50 in this case, is the dose of anti-coagulant required to prolong the prothrombin times by 50%.

2. *Baits*: Baits containing 0.025% or 0.020% anti-coagulant were produced by acetone slurry. After air drying, these were diluted as necessary by hand mixing. The bait base in all cases was medium grade stabilised oatmeal.

20 The prepared baits were offered to rats or mice. No alternative diet was available. Tap water was available ad lib. Baits were replaced daily. Mortality counts were made daily up to 10 days of continuous feeding.

1. PROTHROMBINS

Prothrombin ED 50* 4th day after 3 daily I.P. injections in PEG 300.

Approximate ED 50 mg/Kg/Day x 3 daily doses.

25 Male *Rattus norvegicus*.

modified

TABLE 2

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diet was
Mortality

5
10
15
20
25

Compound	Homozygous Resistant	Wistar	Resistance Factor**
Warfarin S(-)	>50	0.35	>100
Warfarin R(+)	>50	3.50	> 15
Coumatetralyl	$\approx$ 5.0	0.30	$\sim$ 16
Chlorophacinone	$\approx$ 20	0.19	$\sim$ 100
Diphacinone	>20	0.23	> 90
Pival	>20	—	—
1 i	0.4	0.15	2.7
1 iii	0.32	0.15	2.1
1 iv	0.32	0.17	1.9
3	0.45	0.25	1.8
4	0.12	0.12	1.0
5	0.10	0.08	1.3
6	0.40	0.18	2.2
7	0.14	0.09	1.6
8 i	—	0.12	—
8 ii + iii	0.12	0.10	1.2
8 iv	—	0.07	—
9	0.22	0.13	1.7
10	0.07	0.07	1.0
11	—	0.33	—
12	—	0.18	—
13	—	0.20	—

* ED 50 - dose calculated to elevate one stage prothrombin time from a mean resting level of 16 seconds to 112 seconds. Calculated by best line of fit in logarithmic probability paper.

** E.D. 50 Resistant/E.D. 50 Non-Resistant.

50

	<u>Resistant</u>	<u>Normal</u>
Activity of product of Example I i relative to S(-) Warfarin:	> 100 X	~ 2
Activity of product of Example I i relative to Coumatetralyl:	> 10 X	~ 2

2. BAIT TRIALS

10 day continuous exposure no choice.

(a) Resistant female homozygous resistant R. norvegicus.

TABLE 3

Compound	Concentration (ppm)	Mortality	Standards
Warfarin	250	0/10	
Chlorophacinone	250	0/5	
Coumatetralyl	250 200	1/5 1/5	
1 i	20 10 5	5/5 7/10 0/15	
4	10 5	4/5 3/10	
5	10 5 2	5/5 5/5 4/5	
6	50 10	5/5 0/5	
7	5 2	10/10 0/5	
8 ii + iii	5 2 1	5/5 5/5 5/5	
9	5 2	5/5 3/5	
10	5 1	5/5 2/5	
11	50	5/5	
12	10	4/5	
13	10	1/5	

(81)

(b) Non-resistant LAC mice

Compound	Concentration ppm	Mortality
S(-) Warfarin	20	10/10
	10	5/10
	5	2/10
R(+) Warfarin	100	9/10
	20	1/10
	10	0/10
1 i	1.0	10/10
	0.5	15/20
	0.2	0/10
4	0.5	5/10
5	0.5	9/10
6	2.0	10/10
7	1.0	10/10
8 ii + iii	0.5	10/10
9	0.5	9/10
10	0.5	10/10
	0.2	0/10

(c) Resistant Rattus rattus

Compound	Concentration ppm	Mortality
Warfarin	250	0/5
1 i	50	5/5
8 ii	50	5/5

(d) Resistant Mus. musculus

Compound	Concentration ppm	Mortality
Warfarin	250	0/5
1 i	50	5/5
8 ii + iii	50	5/5

Standards

3. Activity of isomers

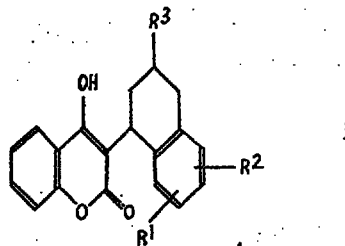
One stage prothrombin times as measured on the fourth day after 3 daily I.P. injections

Male R. norvegicus used throughout.

	Dose mg/Kg/day × 3	Mean Prothrombin seconds
1 fast running isomer Wistar rats	0.3 0.15 0.08	213 126 15
1 fast running isomer Homozygous resistant rats	0.4	24.9
1 slow running isomer Wistar rats	0.15 0.10	190.5 130.0
1 slow running isomer Homozygous resistant rats	0.4 0.2 0.1	212 128.3 28.0
8 fast running isomers (i) Wistar rats	0.2 0.1 0.075	212+ 83.4 40.2
8 slow running isomers (iv) Wistar rats	0.10 0.05 0.02	212+ 73.5 16.7

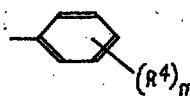
WHAT WE CLAIM IS:—

1. Compounds of general formula:



5

where R^1 and R^2 are the same or different and are hydrogen or halogen atoms or straight or branched chain alkyl or alkoxy groups, R^3 is an aryl group having the formula:



10

where m is 1 or 2, and R^4 is the same or different and is a halogen atom; a straight or branched chain alkyl or alkoxy group; a cycloalkyl group; an aralkyl group; or a phenyl or phenoxy group, or a halogen substituted derivative thereof.

2. Compounds as claimed in claim 1 wherein R^3 is an halogenophenyl group, a bi-phenyl group, an halogeno bi-phenyl group, a phenoxy phenyl group or an halogeno phenoxy phenyl group.



3. Activity of isomers

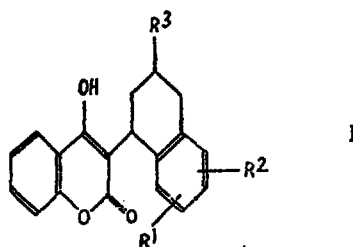
One stage prothrombin times as measured on the fourth day after 3 daily I.P. injections

Male R. norvegicus used throughout.

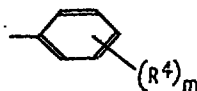
	Dose mg./Kg/day × 3	Mean Prothrombin seconds
1 fast running isomer Wistar rats	0.3 0.15 0.08	213 126 15
1 fast running isomer Homozygous resistant rats	0.4	24.9
1 slow running isomer Wistar rats	0.15 0.10	190.5 130.0
1 slow running isomer Homozygous resistant rats	0.4 0.2 0.1	212 128.3 28.0
8 fast running isomers (i) Wistar rats	0.2 0.1 0.075	212+ 83.4 40.2
8 slow running isomers (iv) Wistar rats	0.10 0.05 0.02	212+ 73.5 16.7

WHAT WE CLAIM IS:—

1. Compounds of general formula:



- 5 where R^1 and R^2 are the same or different and are hydrogen or halogen atoms or straight or branched chain alkyl or alkoxy groups, R^3 is an aryl group having the formula:



- 10 where m is 1 or 2, and R^4 is the same or different and is a halogen atom; a straight or branched chain alkyl or alkoxy group; a cycloalkyl group; an aralkyl group; or a phenyl or phenoxy group, or a halogen substituted derivative thereof.

2. Compounds as claimed in claim 1 wherein R^3 is an halogenophenyl group, a bi-phenyl group, an halogeno bi-phenyl group, a phenoxy phenyl group or an halogeno phenoxy phenyl group.

10



3. Compounds as claimed in claim 2 wherein R³ is a 4-chlorophenyl group, a 4-bromophenyl group, a 4-(4'-chloro)biphenyl group, a 4-(4'-bromo) biphenyl group, a 4-(4'-bromo) phenoxy phenyl group, or a 4-(4'-chloro) phenoxy phenyl group.

4. 3 - (7 - Chloro - 3 - *p* - biphenyl - 1,2,3,4 - tetrahydronaphth - 1 - yl) - 4 - hydroxycoumarin.

5. 3 - (7 - Methyl - 3 - *p* - biphenyl - 1,2,3,4 - tetrahydronaphth - 1 - yl) - 4 - hydroxycoumarin.

6. 3-(3-*p*-biphenyl-1,2,3,4-tetrahydronaphth-1-yl)-4-hydroxycoumarin.

7. 3-(3-*p*-phenoxyphenyl-1,2,3,4-tetrahydronaphth-1-yl)-4-hydroxycoumarin.

8. 3 - (3 - [4' - bromobiphen - 4 - yl] - 1,2,3,4 - tetrahydronaphth - 1 - yl) - 4 - hydroxycoumarin.

9. 3-(3-*p*-chlorophenyl-1,2,3,4-tetrahydronaphth-1-yl)-4-hydroxycoumarin.

10. 3 - (3 - [4' - chlorobiphen - 4 - yl] - 1,2,3,4 - tetrahydronaphth - 1 - yl) - 4 - hydroxycoumarin.

11. 3-(3-*p*-bromophenyl-1,2,3,4-tetrahydronaphth-1-yl)-4-hydroxycoumarin.

12. 3 - (3 - [4 - (*p* - bromophenoxy)phenyl] - 1,2,3,4 - tetrahydronaphth - 1 - yl) - 4 - hydroxycoumarin.

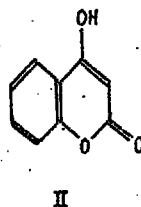
13.-(*p*-cyclohexylphenyl-1,2,3,4-tetrahydronaphth-1-yl)-4-hydroxycoumarin.

14. 3-(*p*-benzylphenyl-1,2,3,4-tetrahydronaphth-1-yl)-4-hydroxycoumarin.

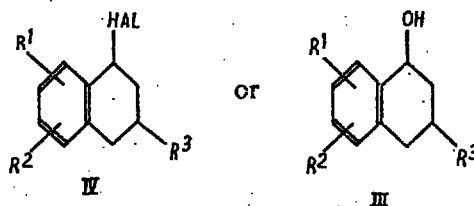
15. 3-(*p*-*n*-hexylphenyl-1,2,3,4-tetrahydronaphth-1-yl)-4-hydroxycoumarin.

16. Compounds as claimed in any one of claims 1 to 15 and substantially as hereinbefore described.

17. A method of making chemical compounds as claimed in any one of claims 1 to 16 comprising condensing a compound of the formula:—

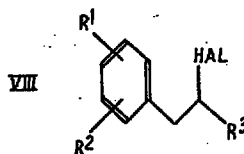


with a compound of the general formula:—

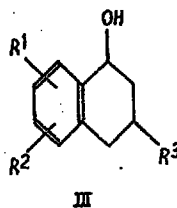


where R¹, R² and R³ are as defined in claim 1 and Hal is halogen.

18. A method as claimed in claim 17 wherein the compound of the general formula:—



is made by reacting a compound of the general formula:—

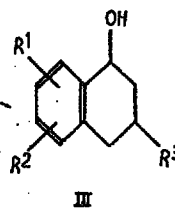


with a halogenating agent.

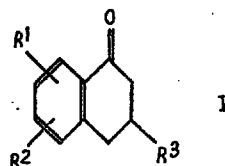


19. A method as claimed in claim 18 wherein the halogenating agent is phosphorus trichloride, phosphorus tribromide or thionyl chloride.

20. A method as claimed in any one of claims 17 to 19 wherein the compound of the general formula:—



is made by reducing a compound of the general formula:—



where R¹, R² and R³ are as defined in claim 1.

21. A method as claimed in any one of claims 17 to 20 substantially as hereinbefore described in the Examples.

22. Compounds as claimed in any one of claims 1 to 16, whenever made by the process claimed in any one of claims 17 to 21.

23. A rodenticidal composition comprising a compound as claimed in any one of claims 1 to 16 and 22 in combination with a carrier.

24. A method of killing rodents comprising feeding the rodents with an effective amount of the composition claimed in claim 23.

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