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PATENT SPECIFICATION

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- (72) The inventor of this invention in the sense of being the actual deviser thereof within the meaning of Section 16 of the Patents Act, 1949, is EUGENE MICHAEL GRIVSKY of Linden Road (P.O. Box 2571), Chapel Hill, North Carolina 27514 USA, a citizen of the United States of America.

(54) CINNAMAMIDES, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(71) We, THE WELLCOME FOUNDATION LIMITED, of 183-193 Euston Road, London, N.W.1., a company incorporated in England, do hereby declare the invention which was communicated from Burroughs Wellcome Co., of 3030 Cornwallis Road, Research Triangle Park, North Carolina 27709, being incorporated in the State of North Carolina, United States of America, 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:—

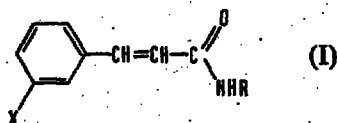
This invention is concerned with chemicals which have valuable pharmacological properties. In particular, the invention concerns cinnamamides, their synthesis, pharmaceutical preparations containing them, and their use in medicine.

It has been found that the cinnamamides of formula (I), as defined below, have anti-convulsant activity in mammals as is shown by their effects upon mice when administered to them in established pharmacological tests. These tests are:—

1. Maximal Electroshock Test (MES) in mice, a method described by Woodbury and Davenport, Arch int. Pharmacodyn. Ther. 92, P. 97—107 (1952).

2. Metrazol Seizure Test (MET) in mice, a method described by Swinyard, Brown and Goodman, J. Pharmacol. Exp. Therap. 106, 319—330 (1952).

In formula (I)



X is chlorine, bromine or iodine, and R is hydrogen or alkyl having 1 to 3 carbon atoms. The *trans* configuration of the compounds of formula (I) is preferred; and the compound wherein R is ethyl and X is bromine has outstanding anti-convulsant activity in both pharmacological tests described above. Other examples of compounds within the scope of formula (I) include:

- 3-Bromo-N-methylcinnamamide
- 3-Bromo-N-n-propylcinnamamide
- 3-Bromo-N-isopropylcinnamamide
- 3-Chloro-N-methylcinnamamide
- 3-Chloro-N-ethylcinnamamide
- 3-Chloro-N-n-propylcinnamamide

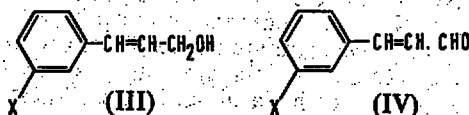
The compounds of formula (I) may be made by any method known for the synthesis of cinnamamides of analogous structure. For example they may be prepared by the acylation of an amine RNH₂, (wherein R is hydrogen or alkyl having 1 to 3 carbon atoms) by the corresponding acid of formula (II):



(wherein X has the meaning given for formula (I)) or a reactive derivative thereof such as a thioester or an ester (e.g. an alkyl ester or alkylthioester where the alkyl has e.g. 1 to 4 carbon atoms), an amide, an acid halide (e.g. an acid chloride) or an acid anhydride. A wide variety of reaction conditions may be employed depending upon the nature of the acylating agent, but in general the reactants may be refluxed together, preferably in an inert liquid medium such as ether, benzene, toluene or cyclohexane.

A most convenient method of synthesis is to react the acid chloride with the appropriate amine. Preferably one equivalent of the halide should be used with two or more equivalents of the amine, but the molar excess of the amine may be replaced by another base such as triethylamine, pyridine, dimethylaniline, or potassium or sodium carbonate. A wide variety of polar or non-polar liquid media may be used including water, alkanols such as methanol and ethanol, diethylether, dioxane, benzene, toluene, xylene, petroleum ether, cyclohexane, tetrahydrofuran, chloroform and carbon tetrachloride. A wide range of temperature conditions may be employed, for example from -10°C . to the reflux temperature of the reaction mixture.

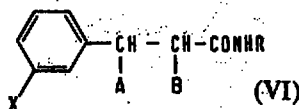
The compounds of formula (I) may be further prepared directly from the corresponding alcohol or aldehyde of formula (III) and (IV) at a temperature below 10°C .



wherein X has the meaning in formula (I), by reaction with the appropriate amine RNH_2 in the presence of nickel peroxide and an inert liquid medium such as diethylether, benzene, tetrahydrofuran, or a petroleum hydrocarbon.

The compounds of formula (I) may also be made by the reaction of an amide of formula (V): R.NH.W wherein R is as hereinbefore defined and W is a leaving group, for example $-\text{CO.H}$ (a formamide), $-\text{CO.alkyl}$ where the alkyl has e.g. 1 to 4 carbon atoms (an amide), $-\text{CONH}_2$ (urea), $-\text{COO.alkyl}$ (urethane having 1—4 carbon atoms in the alkyl group), with an acid of formula (II) or a reactive derivative thereof, for example the acid anhydride or halide such as the acid chloride. When the anhydride is used, a catalytic amount of sulphuric acid is preferably included. The reactants are conveniently heated together in a liquid medium.

In a further method for making a compound of formula (I), water, a hydrogen halide or molecular halogen is eliminated from a compound of formula (VI)



wherein A and B are the same and each is halogeno or one of A and B is halogeno or hydroxy and the other is hydrogen, and X and R have the meaning given in formula (I) above. For example, the elimination of water from the α - or β -hydroxy compounds of formula (VI) may be effected by reaction with a dehydrating agent such as a base (e.g. aqueous sodium hydroxide) or concentrated sulphuric or polyphosphoric acid. The monohalo intermediates may be treated with a base (e.g. potassium hydroxide or *N,N*-dimethylaniline) or merely heated to release the hydrogen halide. The dihalo intermediates may be reduced, for example with zinc and ethanol or converted to the diiodo compounds by treatment with potassium iodide with subsequent release of molecular iodine.

The intermediate acids of formula (II) may be made by classical organic synthetic methods such as the Perkin synthesis, the Reformatsky reaction and the Knoevenagel condensation.

The compounds of formula (I) may be used for the treatment or prophylaxis of convulsions of mammals such as mice, dogs and cats, and more importantly of man. In particular they may be used in the treatment of grand mal, petit mal,

psychomotor epilepsy and focal seizures at a dose of 2 to 200 mg/kg of body weight per day. The optimum dose of course will vary with the nature of the compound, the condition of the patient and the route of administration, but the preferred dose is in the range of 20 to 60 mg/kg, most conveniently 30 to 50 mg/kg body weight, per day. Administration of the desired daily dose is preferably in three divided doses. For example, convenient forms of administration include tablets each containing from 100 to 500 mg of a compound of formula (I).

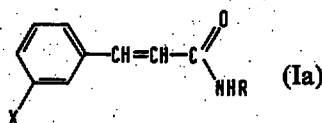
For use in medicine the compounds of formula (I) may be administered as a pure chemical but are preferably presented with an acceptable carrier thereof as a pharmaceutical composition. The carrier must be of course be 'acceptable' in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient of the composition. The carrier may be a solid or a liquid or a mixture of solid and liquid substances, and is preferably formulated with a compound of formula (I) as a unit-dose composition, for example a tablet, capsule or sachet for oral administration or a suppository for rectal administration. Other pharmaceutically active substances may also be present in compositions of the present invention and the composition may be formulated by any of the well known techniques of pharmacy consisting basically of admixture of its components. Unit-dose compositions, for oral, rectal or parenteral administration (*vid. inf.*), conveniently contain a compound of formula (I) in an amount in the range 100 to 500 mg.

For oral administration, fine powders or granules of the compounds may contain diluents and dispersing and surface active agents, and may be presented in a draught in water or in a syrup; in capsules or cachets in the dry state or in an aqueous or non-aqueous suspension, when a suspending agent may also be included; in tablets, preferably made from granules of the active ingredient with a diluent, by compression with binders and lubricants; or in a suspension in water or a syrup or an oil or in a water/oil emulsion, when flavouring, preserving, suspending, thickening and emulsifying agents may also be included. The granules or the tablets may be coated, and the tablets may be scored.

For parenteral administration (by intramuscular or intraperitoneal injection), the compounds may be presented in unit dose or multi-dose containers in aqueous or non-aqueous injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the compounds isotonic with the blood; or in aqueous or non-aqueous suspensions when suspending agents and thickening agents may also be included; extemporaneous injection solutions and suspensions may be made from sterile powders, granules or tablets which may contain diluents, dispersing and surface active agents, binders and lubricants.

The invention therefore comprises:—

a) A compound of the formula (Ia)



wherein X is chlorine, bromine or iodine and R is hydrogen or alkyl having 1 to 3 carbon atoms, except that when X is chloride R is other than hydrogen.

b) A compound of the formula (Ia) having the *trans* configuration.

c) 3-Bromo-N-ethylcinnamamide.

d) The synthesis of a compound of formula (Ia) by any known method and in particular the method specifically described above and including the reaction of an acid $m\text{-X-PhCH=CHCO}_2\text{H}$ or a reactive derivative thereof with a compound of the formula R.NH.W wherein W is a leaving group and R and X have the meaning in formula (Ia).

e) A pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier thereof.

f) A method for the treatment or prophylaxis of convulsions of a mammal other than human comprising the administration to the mammal of an anti-convulsant effective, non-toxic amount of a compound of formula (I).

g) A method for preparing a composition defined in (e) comprising admixture of the components thereof followed, where appropriate, by disposition of the bulk composition into unit doses thereof.

In formula (I) as above defined all compounds are believed to be novel with

the exception of that wherein X is chlorine and R is hydrogen. This compound is taught in the literature (Chem. Abs., 1970, 72, 21696) as an intermediate in the synthesis of derivatives thereof but has not been ascribed any pharmacological activity.

The following Examples 1 to 10 and 12 to 20 illustrate the present invention but should not be construed as in any way constituting a limitation thereof. Example 11 describes the preparation of the known compound 3-chlorocinnamamide. All temperatures are in degrees Celsius.

Example 1.

Trans-3-bromo-*N*-isopropylcinnamamide

Trans-*m*-bromocinnamic acid (11.4 g) in dry benzene (75 ml) was heated to reflux and then a mixture of thionyl chloride (12 g) in dry benzene (50 ml) was added at such a rate as to maintain constant reflux. The reaction mixture was heated at reflux for an additional 2 hr after the addition of thionyl chloride. The solvent and excess thionyl chloride were then removed under reduced pressure to give *trans*-3-bromocinnamoyl chloride (ca. 12.3 g). A solution of the 3-bromocinnamoyl chloride in toluene (150 ml) was added dropwise with stirring to a solution of isopropylamine (10 g) in ether (200 ml). The reaction mixture was stirred at room temperature for one hour and then heated at reflux for one hour. The solvent and excess amine were removed under reduced pressure. The crude residue was triturated with water, filtered, and recrystallized from ethanol-water to give white, crystalline *trans*-3-bromo-*N*-isopropylcinnamamide, m.p. 85–86°C. Elemental analysis, NMR and IR spectra all confirmed the identity of the product.

Example 2.

Trans-3-bromo-*N*-ethylcinnamamide

A solution of *trans*-3-bromocinnamoyl chloride (12.3 g) in anhydrous toluene (150 ml) was added slowly with stirring to a solution of ethylamine (10 g) in dry ether (100 ml) at room temperature. The reaction mixture was heated at reflux for one hour, and the solvent and excess amine were then removed under reduced pressure. The residue was triturated with water, filtered, and recrystallized from ethanol-water to give *trans*-3-bromo-*N*-ethylcinnamamide, m.p. 89–90°C., as a white crystalline material. NMR and IR spectra as well as elemental analysis were consistent with the assigned structure.

Example 3.

Trans-3-Bromo-*N*-ethylcinnamamide

Trans-*m*-bromocinnamic acid (14.8 g), ethanol (173 ml) and concentrated sulfuric acid (0.4 ml) were combined and heated at reflux for 15 hours. About 150 ml of the ethanol was distilled off, and the remaining solution was poured into ice/water (140 ml). The cold mixture was made strongly alkaline with 40% w/v sodium hydroxide and extracted with methylene chloride (4 × 60 ml). The combined methylene chloride extract was dried over anhydrous potassium carbonate. The potassium carbonate was removed by filtration and the solvent stripped off under reduced pressure. Ethyl *trans*-3-bromocinnamate, was obtained as a partially solidified oil. (IR spectrum was consistent with this compound).

Ethyl *trans*-3-bromocinnamate (8.4 g), ethylamine (6.7 g), methanol (18 ml) and 4A molecular sieves (1 g) were combined and heated at reflux for 1/2 hour. The mixture was cooled to about 45°C and sodium methoxide (0.6 g) added. The mixture was then heated at reflux 1-1/2 hour and then cooled. It was acidified with concentrated hydrochloric acid (12 ml). The sieves were removed by filtration. Ice water was added to the filtrate to precipitate *trans*-3-bromo-*N*-ethylcinnamamide, m.p. 89–90°C (after recrystallization from ethanol/water).

Example 4.

Trans-3-bromo-*N*-methylcinnamamide

A solution of *trans*-3-bromocinnamoyl chloride (5 g) in dry benzene (100 ml) was added with stirring to an ethereal (200 ml) solution of methylamine (3 g). After the addition was complete, a slow stream of methylamine gas was bubbled through the reaction mixture at room temperature for one hour. Solvent and excess amine were removed under reduced pressure. The crude product was triturated with water, filtered, and recrystallized from ethanol-water to give *trans*-3-bromo-*N*-methylcinnamamide, m.p. 147–147.5°C. NMR, IR, and elemental analysis were consistent with this structure.

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Example 5.

Trans-3-chloro-*N*-ethylcinnamamide

Trans-3-chlorocinnamoyl chloride (4.4 g) in dry benzene (75 ml) was allowed to react with an excess of ethylamine in dry ether (75 ml) according to the procedure of Example 2. *Trans*-3-chloro-*N*-ethylcinnamamide, m.p. 87—88°C, was obtained which had NMR, IR, and elemental analysis consistent with this structure.

Example 6.

Trans-3-iodo-*N*-ethylcinnamamide

Trans-*m*-iodocinnamoyl chloride was prepared from *trans*-*m*-iodocinnamic acid according to the standard procedure exemplified in Example 1. The acid chloride (6.6 g) in dry toluene (200 ml) was added with stirring to a solution of ethylamine (3.0 g) in dry ether (300 ml) at room temperature. The reaction mixture was heated at reflux for one hour and then worked up according to Example 2 to yield *trans*-*m*-iodo-*N*-ethylcinnamamide, m.p. 116—117°C as a white, crystalline material. NMR, IR and elemental analysis were consistent with this structure.

Examples 7—11.

Following the procedure of Example 2, the following *trans* compounds were prepared (in all cases the NMR and IR spectra and elemental analysis confirmed the structure) in which X and R have the values in formula (I):—

Example	X	R	m.p. (°C)
7	Cl	CH ₃	124—125
8	Cl	CH ₂ CH ₂ CH ₃	78—79
9	Br	CH ₂ CH ₂ CH ₃	84—85
10	Br	H	107—108
11 *	Cl	H	81—82

* C.A. 1970, 72, 21696

Example 12.

A suppository was formulated from the following ingredients:

<i>trans</i> -3-Bromo- <i>N</i> -ethylcinnamamide	300 mg
Coaco butter	2000 mg

Example 13.

A shoft gelatin capsule was filled with the following ingredients:

<i>trans</i> -3-Bromo- <i>N</i> -ethylcinnamamide	300 mg
Lactose	75 mg
Starch, corn	20 mg
Fused silica	2 mg
Magnesium stearate	3 mg

Example 14.

A syrup suspension was prepared from the following ingredients:

<i>trans</i> -3-Bromo- <i>N</i> -ethylcinnamamide	300 mg
Sodium carboxymethylcellulose	20 mg
Microcrystalline cellulose	100 mg

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Glycerin	500 mg
Polysorbate 80	10 ml
Flavouring agent	Q.S.
Preserving agent	0.1%
Sucrose syrup	Q.S. to 5 ml

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Example 15.

A compressed tablet was prepared from the following:

<i>trans</i> -3-Bromo- <i>N</i> -ethylcinnamamide	300 ml
Corn starch	50 mg
Microcrystalline cellulose	50 mg
Stearic acid	4 mg
Magnesium stearate	1 mg
Fused silica	1 mg

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Example 16.

In the MES pharmacological test referred to hereinbefore, *trans*-3-bromo-*N*-ethylcinnamamide had an oral ED₅₀ in the mouse and rat of 80 mg/kg and 26 mg/kg respectively.

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Example 17.

Anticonvulsant activity was determined in mice using the Maximal Electroshock Test (MES) performed according to the method of Woodbury and Davenport, *supra*, with corneal electrodes and a Wahlquist Electroshock Stimulator Model E (manufactured by Wahlquist Instrument Co., Salt Lake City, Utah.).

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Trans-3-bromo-*N*-ethylcinnamamide was suspended in 0.5% aqueous methylcellulose by homogenation in a tissue homogenization grinder to give a particle size size such that greater than 51% was less than 5 microns and greater than 87% was less than 20 microns to give concentrations of 5, 7.5, 10, 15 and 20 mg of compound per ml of methylcellulose solution. The mice, male, ICR Blue Spruce of 22 g average weight, were divided into six groups of ten mice each. The *trans*-3-bromo-*N*-ethylcinnamamide suspensions were administered one hour prior to test orally (p.o.) by direct injection into the stomachs of the mice. The control mice received an equivalent volume of p.o. aqueous 0.57 methylcellulose one hour prior to test.

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A current of 50 ma was applied to the cornea of the mice for 0.2 second and the time elapsed between application of the electric shock and hind limb extensor seizure (convulsive extension of the hind legs) measured and recorded as latency of hind limb extension. Animals were considered protected (p) if the hind limb extensor component of the convulsion was blocked. An increase over the control in mean latencies is also indicative of anti-convulsant activity.

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The results are shown in the following Table.

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TABLE

Dose, mg/kg;	Latency of Hind Limb Extension (seconds)					
	0 (Control)	50	75	100	150	200
Mice in Group	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
1	1.8	p	p	1.2	p	p
2	2.0	p	2.8	4.8	p	p
3	1.5	1.8	3.3	p	p	p
4	1.8	1.8	2.1	2.2	p	p
5	1.2	1.2	3.2	p	p	p
6	1.2	1.2	p	p	p	p
7	1.2	p	1.8	1.8	p	p
8	1.8	1.2	2.8	p	p	p
9	1.8	1.2	p	p	p	p
10	1.8	2.2	p	1.5	p	p
% protected	0	30	40	50	100	100
Mean Latency	1.61	1.51	2.66	2.30	—	—

The above test results (% protected) demonstrates that *trans*-3-bromo-*N*-ethylcinnamamide is effective in preventing convulsive hind limb extension due to electrical shock in mice.

Each group comprised 10 mice. A different group was used for each dosage. p indicates protected against electrical shock.

Examples 18 and 19.

Following the procedure of Examples 1 and 4 respectively, using *trans*-3-iodocinnamoyl chloride, the following *trans* compounds were prepared in which X and R have the values in formula (I):

Example	X	R	m.p. (°C.)
18	I	CH(CH ₃) ₂	109—110
19	I	H	134—135

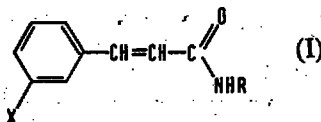
In each case IR and UV spectra and elemental analysis confirmed the structure. The melting points listed are after recrystallization from ethanol-water.

Example 20.

Investigation of the compound *trans*-3-bromo-*N*-ethylcinnamamide (Examples 2 and 3) using the techniques of differential scanning calorimetry and hot stage microscopy (for melting point behaviour) revealed the existence of two physically different crystalline forms (polymorphs), for convenience identified as Form I and Form II respectively. Form II melted in the range 86—87°C and could be converted by grinding to Form I which melted in the range 88°—90°C.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising a compound of formula (I)



wherein X is chlorine, bromine or iodine and R is hydrogen or alkyl having 1 to 3 carbon atoms, together with a pharmaceutically acceptable carrier therefor.

2. A composition according to claim 1 wherein, in the compound of formula (I), X is chlorine, bromine or iodine and R is alkyl having 1 to 3 carbon atoms.

3. A composition according to claim 1 wherein, in the compound of formula (I), X is bromine or iodine and R is hydrogen.

4. A composition according to claim 1 wherein the compound of formula (I) is 3-bromo-*N*-ethylcinnamamide.

5. A composition according to any of claims 1 to 4 wherein the compound of formula (I) has the *trans* configuration.

6. A composition according to claim 1 wherein the compound of formula (I) is *trans*-3-bromo-*N*-ethylcinnamamide.

7. A composition according to any of claims 1 to 6 wherein the carrier is a solid.

8. A composition according to any of claims 1 to 6 wherein the carrier is a liquid.

9. A sterile, injectable composition according to claim 8.

10. A composition according to any of claims 1 to 8, suitable for administration by the oral or rectal route.

11. A composition according to any of claims 1 to 10 in unit-dose form.

12. A composition according to claim 11 which is an orally ingestible tablet.

13. A unit-dose composition according to either of claims 11 and 12 which contains a compound of formula (I) in an amount in the range 100 to 500 mg.

14. A composition according to any of claims 1 to 6 which comprises a suspension of a compound of formula (I) in an orally ingestible liquid carrier.

15. A method for the preparation of a composition according to any of claims 1 to 14 which comprises admixture of the components thereof followed, where appropriate, by disposition of the bulk composition into unit doses thereof.

16. A compound of formula (I) as defined in either of claims 2 and 3.

17. 3-Bromo-*N*-isopropylcinnamamide.

18. 3-Bromo-*N*-methylcinnamamide.

19. 3-Chloro-*N*-ethylcinnamamide.

20. 3-Iodo-*N*-ethylcinnamamide.

21. 3-Chloro-*N*-methylcinnamamide.

22. 3-Chloro-*N*-*n*-propylcinnamamide.

23. 3-Bromo-*N*-*n*-propylcinnamamide.

24. 3-Bromocinnamamide.

25. 3-Iodo-*N*-isopropylcinnamamide.

26. 3-Iodocinnamamide.

27. 3-Bromo-*N*-ethylcinnamamide.

28. The *trans* isomer of a compound according to any of claims 16 to 27.

29. *Trans*-3-bromo-*N*-ethylcinnamamide.

30. A method for the preparation of a compound according to any of claims 16 to 29 which comprises reaction of an amine R.NH₂ with an acid of formula (II):



or a reactive derivative thereof, wherein R and X have the meanings defined in formula (I).

31. A method according to claim 30 wherein the reactive derivative of the acid of formula (II) is selected from an amide, an acid halide, the acid anhydride, and an alkyl ester or alkyl thioester where in each case the alkyl has 1 to 4 carbon atoms.

32. A method according to claim 31 wherein the acid halide is the acid chloride.

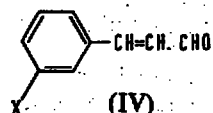
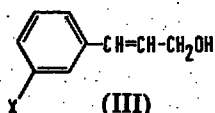
33. A method according to claim 30 for the preparation of *trans*-3-bromo-*N*-



ethylcinnamamide which comprises reaction of ethyl *trans*-3-bromocinnamate with ethylamine.

34. A method according to claim 30 for the preparation of *trans*-3-bromo-*N*-ethylcinnamamide which comprises reaction of *trans*-3-bromocinnamoyl chloride with ethylamine.

35. A method for the preparation of a compound according to any of claims 16 to 29 which comprises reaction of an amine $R.NH_2$ with an alcohol or aldehyde of formula (III) or (IV) respectively,



wherein R and X have the meanings defined in formula (I), in the presence of nickel peroxide and an inert liquid medium at a temperature below 10°C.

36. A method for the preparation of a compound according to any of claims 16 to 29 which comprises reaction of a compound of formula (V): $R.NH.W$ with an acid of formula (II):



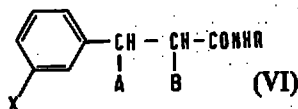
or a reactive derivative thereof, wherein R and X have the meanings defined in formula (I) and W is a leaving group.

37. A method according to claim 36 wherein the leaving group W is selected from $-CO.H$, $-CONH_2$, $-CO.Alkyl$ and $-COO.Alkyl$ where in each case Alkyl has 1 to 4 carbon atoms.

38. A method according to either of claims 36 and 37 wherein the reactive derivative of the acid of formula (II) is selected from the acid anhydride and an acid halide.

39. A method according to claim 38 wherein the acid halide is the acid chloride.

40. A method for the preparation of a compound according to any of claims 16 to 29 which comprises elimination of the elements of water, a hydrogen halide or molecular halogen, as appropriate, from a compound of formula (VI)



wherein A and B are the same and each is halogeno or one of A and B is halogeno or hydroxy and the other is hydrogen, and R and X have the meanings defined in formula (I).

41. A method according to claim 40 wherein one of A and B is hydroxy and the other is hydrogen and the compound of formula (VI) is reacted with a dehydrating agent.

42. A method according to claim 40 wherein one of A and B is halogeno and the other is hydrogen and the compound of formula (VI) is treated with a base or is heated.

43. A method according to claim 40 wherein A and B are the same and each is halogeno and the compound of formula (VI) is treated with a reducing agent or, where A and B are other than iodo, the compound of formula (VI) is converted to the corresponding diiodo compound by treatment with potassium iodide with subsequent release of molecular iodine to yield the compound of formula (I).

44. A compound according to any of claims 16 to 29 when prepared by a method claimed in any of claims 30 to 43.

45. *Trans*-3-bromo-*N*-ethylcinnamamide when prepared by a method claimed in either of claims 33 and 34.

46. A method for the treatment of prophylaxis of convulsions of a mammal other than human comprising the administration to the mammal of an anti-convulsant effective, non-toxic amount of a compound defined in any of claims 1 to 6 and 16 to 29.



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47. A method according to claim 46 wherein the convulsions are selected from grand mal, petit mal, psychomotor epilepsy and focal seizures.

48. A method according to either of claims 46 and 47 wherein the compound is administered by the oral route.

5 49. A method according to any of claims 46 to 48 wherein the compound is *trans*-3-bromo-*N*-ethylcinnamamide.

50. A method according to any of claims 46 to 49 wherein the compound is administered at a dose of 2 to 200 mg/kg mammal body weight per day.

10 51. A method substantially as hereinbefore described, with reference to Examples 1 to 10 and 18 and 19, for the preparation of a compound according to any of claims 16 to 29.

52. A pharmaceutical composition as defined in any of claims 1 to 14 substantially as hereinbefore described with reference to Examples 12 to 15 and 17.

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