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(19)

(54) BIOLOGICALLY ACTIVE AMIDES

(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:—

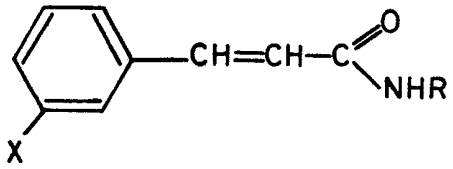
This invention is concerned with chemicals which have valuable pharmacological properties. In particular, the invention concerns cinnamamides, their synthesis, pharmaceutical preparations containing them, and their use in medicine.

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):



(I)

X is fluoro, chloro, bromo, iodo or trifluoromethyl; and

R is branched alkyl having 4 to 8 carbon atoms, cycloalkyl having 3 to 8 carbon atoms, cycloalkylalkyl wherein the cycloalkyl moiety has from 3 to 8 carbon atoms and the alkyl moiety has 1 to 3 carbon atoms, and when X is fluoro or trifluoromethyl then R may also be hydrogen or alkyl having 1 to 3 carbon atoms.

The compounds of formula (I) having the *trans* configuration are preferred.

A subclass of compounds within formula (I) are those compounds wherein X is fluoro or trifluoromethyl and R is hydrogen or alkyl having 1 to 3 carbon atoms.

A further subclass of compounds within formula (I) are these wherein X is fluoro, chloro, bromo, iodo or trifluoromethyl and R is branched alkyl having 4 to 8 carbon atoms. Suitable branched alkyl groups include *iso* butyl, *sec* butyl, *t* butyl and those of the higher homologues pentyl, hexyl, heptyl and octyl.

A still further subclass of compounds of formula (I) are those compounds wherein X is fluoro, chloro, bromo, iodo or trifluoromethyl and R is cycloalkyl having 3 to 8 carbon atoms, and these wherein the cycloalkyl moiety has 3 to 6 carbon atoms; in particular may be mentioned those compounds wherein R is cyclopropyl.

Also included in formula (I) is the subclass of compounds wherein R is cycloalkylalkyl.

Among the compounds within formula (I) may specifically be mentioned:—

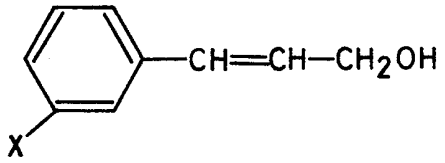
3-fluorocinnamamide;
3-fluoro-*N*-ethylcinnamamide;
3-fluoro-*N*-*iso*-propylcinnamamide;
3-fluoro-*N*-cyclopropylcinnamamide;
3-fluoro-*N*-cyclopentylcinnamamide;
3-fluoro-*N*-cyclohexylcinnamamide;
3-fluoro-*N*-cycloheptylcinnamamide;
3-fluoro-*N*-cyclooctylcinnamamide;
3-fluoro-*N*-cyclobutylcinnamamide;
3-chloro-*N*-*iso*-butylcinnamamide;
3-chloro-*N*-cyclopropylcinnamamide;
3-chloro-*N*-cyclopentylcinnamamide;
3-chloro-*N*-cyclohexylcinnamamide;
3-chloro-*N*-cycloheptylcinnamamide;
3-chloro-*N*-cyclooctylcinnamamide;
3-chloro-*N*-cyclobutylcinnamamide;
3-bromo-*N*-*iso*-butylcinnamamide;
3-bromo-*N*-cyclopropylcinnamamide;
3-bromo-*N*-*t*-butylcinnamamide;
3-bromo-*N*-cyclobutylcinnamamide;
3-bromo-*N*-cyclopentylcinnamamide;
3-bromo-*N*-cyclohexylcinnamamide;
3-bromo-*N*-cycloheptylcinnamamide;
3-bromo-*N*-cyclooctylcinnamamide;
3-bromo-*N*-cyclohexylmethylcinnamamide;
3-iodo-*N*-*iso*-butylcinnamamide;
3-iodo-*N*-*t*-butylcinnamamide;
3-iodo-*N*-cyclopropylcinnamamide;
3-iodo-*N*-cyclopentylcinnamamide;
3-trifluoromethylcinnamamide;
3-trifluoromethyl-*N*-methylcinnamamide;
3-trifluoromethyl-*N*-ethylcinnamamide;
3-trifluoromethyl-*N*-*n*-propylcinnamamide;
3-trifluoromethyl-*N*-*iso*-propylcinnamamide;
3-trifluoromethyl-*N*-*iso*-butylcinnamamide;
3-trifluoromethyl-*N*-cyclopropylcinnamamide;
3-trifluoromethyl-*N*-cyclobutylcinnamamide;
3-trifluoromethyl-*N*-cyclopentylcinnamamide;
3-trifluoromethyl-*N*-cyclohexylcinnamamide;
3-trifluoromethyl-*N*-cycloheptylcinnamamide;
3-trifluoromethyl-*N*-cyclooctylcinnamamide; and
3-trifluoromethyl-*N*-cyclohexylmethylcinnamamide.

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 RNH_2 (wherein R is the same as in the formula (I) by the corresponding acid of formula (II): m—X—$PhCH{=}CHCO_2H$ (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 thioester 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.

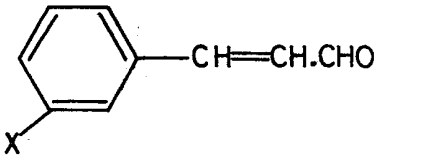
A most convenient method of synthesis is to react the acid chloride with the appropriate amine. Preferably one equivalent of the halide should be used with two or more equivalents of the amine, but the molar excess of the amine may be replaced by another base such as triethylamine, pyridine, dimethylaniline, or potassium or sodium carbonate. A wide variety of polar or non-polar liquid media may be used including water, alkanols such as methanol or ethanol, ether, 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 formulae (III) and (IV) at a temperature below 10°C.



(III)

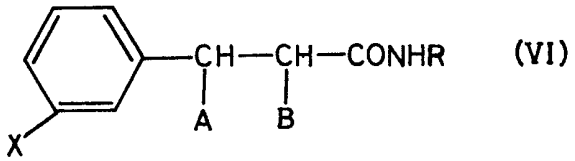


(IV)

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 ether, 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 W is a leaving group, for example —CO . H (a formamide), —CO . alkyl wherein the alkyl has e.g. 1 to 4 carbon atoms (an amide), —$CONH_2$ (urea), —CONHR wherein R has the same meaning as formula (I) (substituted urea, —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. 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 of making a compound of formula (I), water, a hydrogen halide or molecular halogen is eliminated from a compound of formula (VI):



(VI)

wherein A and B are the same and each is halo or one of A and B is halo 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 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. The compound 3-trifluoromethyl-*N*-cyclopropylcinnamamide is particularly valuable for its anticonvulsant properties.

The compounds of formula (I), in particular the compound 3-fluoro-*N*-cyclopropylcinnamamide, may also be used to decrease skeletal muscle tone. For example they may be used to induce relaxation of skeletal muscle in the treatment or prophylaxis of spastic, hypertonic and hyperkinetic conditions associated with disorders due to increased skeletal muscle tone. In particular the compounds may be used in the treatment and symptomatic relief of conditions such as parkinsonism, chorea, arthritis, athetosis, status epilepticus and tetanus and especially in the relief of muscle spasm in conditions such as myositis, spondylitis, cerebral palsy and multiple sclerosis.

For the treatment or prophylaxis of convulsions, or for decreasing muscular tone, the compounds of formula (I) may be used at a dose of from 2 to 200 mg/kg of bodyweight 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 from 20 to 60 mg/kg, most conveniently from 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 therefor as a pharmaceutical composition. The carrier must 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 cachet 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 an orally ingestible liquid carrier, such as 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.

It will be understood from the foregoing description that what we will claim in accordance with this invention comprises any novel feature described herein, principally but not exclusively as follows:—

(a) Novel compounds of formula (I) hereinabove defined.

(b) Novel compounds of formula (I) hereinabove defined having the *trans* configuration.

(c) The synthesis of a novel compound of formula (I) by any known method and in particular the methods specifically described above and including the reaction of an acid *m*—X—PhCH=CHCO$_2$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 (I).

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

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

(f) A method of decreasing skeletal muscle tone in a mammal excluding man which comprises administration to said mammal of a non-toxic effective tone decreasing amount of a compound of formula (I).

It should be understood that excluded from the scope of the pharmaceutical compositions provided by the present invention are non-sterile mixtures which are mere solutions or suspensions of the known compound of formula (I) as hereinabove defined in solvents and liquids known in the literature for use in the synthesis and/or isolation of the compound by the methods described therein. Included within the scope of the present invention are such solutions and suspensions of the known compound which are pharmaceutically acceptable to the intended recipient thereof and which contain in addition at least one other pharmaceutically acceptable substance.

The following Examples illustrate the present invention but should not be construed as in any way constituting a limitation thereof. All temperatures are in degrees Celsius.

EXAMPLE 1

Trans 3-Bromo-N-cyclopropylcinnamamide

A mixture of trans 3-bromocinnamic acid (m.p. 177—179°; 11.4 g), thionyl chloride (11.9 g) and dry benzene (150 ml) was heated at reflux for 2 hrs. Solvent and excess thionyl chloride were removed by distillation under reduced pressure leaving trans 3-bromocinnamoyl chloride (12.2 g), b.p. 100—100.5°/0.2 mm Hg.

A solution of trans 3-bromocinnamoyl chloride (12.2 g) in dry toluene (150 ml) was added dropwise (rapidly) with rapid stirring to a solution of cyclopropylamine (6.3 g) in dry toluene (150 ml). The reaction mixture was stirred at room temperature for 2 hrs., then at 30—35° for an additional hour; and the solvent and excess amine were removed under reduced pressure. The residue was triturated with water to remove cyclopropylamine hydrochloride. The product was filtered, washed with dilute hydrochloric acid and then with water. It was then recrystallized from ethanol:water (1:10) to give white crystalline trans 3-bromo-N-cyclopropylcinnamamide m.p. 110—111°. Elemental analysis, NMR and IR data were all consistent with the assigned structure. TLC gave one spot run on silica gel with 5:1 and with 3:1 hexane:ethanol.

EXAMPLE 2

Trans 3-Fluoro-N-cyclopropylcinnamamide

A mixture of 3-fluorobenzaldehyde (40 g), malonic acid (47 g), and an ethanolic solution (150 ml) containing pyridine (10 g) and piperidine (5 g) was heated at reflux with stirring for 8 hrs. The reaction mixture was chilled and water (300 ml) was added, giving crystalline trans 3-fluorocinnamic acid which was removed by filtration, washed with water and dried. The trans 3-fluorocinnamic acid, m.p. 162—163°, was obtained in 84% yield.

A mixture of trans 3-fluorocinnamic acid (32.3 g), thionyl chloride (48 g) and dry benzene (300 ml) was heated at reflux for 2 hrs. Solvent and excess thionyl chloride were removed by distillation under reduced pressure leaving trans 3-fluorocinnamoyl chloride as an oil.

A solution of trans 3-fluorocinnamoyl chloride (3.3 g) in dry toluene (100 ml) was added with stirring to a solution of cyclopropylamine (2.5 g) in dry ether (100 ml) at ambient temperature. The reaction mixture was heated at 30—34° for 2 hrs., and the solvent and excess amine were removed under reduced pressure. The residue was triturated with water, filtered and recrystallized from ethanol:water (1:10) to give trans 3-fluoro-*N*-cyclopropylcinnamamide, m.p. 90—91°. Elemental analysis, NMR and IR confirmed the structure. TLC gave one spot run on silica gel with 5:1 and with 3:1 hexane:ethanol.

EXAMPLE 3

Trans 3-Trifluoromethyl-N-Cyclopropylcinnamamide

Using a method analogous to that described in Examples 2 and 3, 3-trifluoromethylcinnamoyl chloride was reacted with cyclopropylamine to give *trans* 3-trifluoromethyl-*N*-cyclopropylcinnamamide, m.p. 73°.

EXAMPLE 4

Trans 3-Bromo-N-iso-butylcinnamamide

Using a method analogous to that described in Examples 2 and 3, 3-

bromocinnamoyl chloride was reacted with isobutylamine to give *trans* 3-bromo-*N*-isobutylcinnamamide, m.p. 104—105°.

EXAMPLE 5
Trans 3-Fluoro-N-cinnamamide

A mixture of 3-fluorobenzaldehyde (40 g), malonic acid (47 g), and an ethanolic solution (150 ml) containing pyridine (10 g) and piperidine (5 g) was heated at reflux with stirring for 8 hrs. The reaction mixture was chilled and water (300 ml) was added, giving crystalline trans 3-fluorocinnamic acid which was removed by filtration, washed with water and dried. The trans 3-fluorocinnamic acid, m.p. 162—163°, was obtained.

A mixture of trans 3-fluorocinnamic acid (32.3 g), thionyl chloride (48 g) and dry benzene (300 ml) was heated at reflux for 2 hrs. Solvent and excess thionyl chloride were removed by distillation under reduced pressure leaving trans 3-fluorocinnamoyl chloride as an oil.

Dry ammonia was passed slowly into a solution of trans 3-fluorocinnamoyl chloride (5.7 g) in dry toluene (50 ml) with rapid stirring until ammonium chloride was no longer formed. The reaction mixture was stirred at ambient temperature for an additional 30 minutes. The solvent and excess ammonia were then removed under reduced pressure and the residual product triturated with water. Recrystallization from ethanol:water (1:10) gave trans 3-fluorocinnamamide, m.p. 121—122°. Elemental analysis, NMR and IR data were consistent with the assigned structure. TLC gave one spot run on silica gel using 5:1 and using 3:1 hexane:ethanol.

EXAMPLE 6

A suppository was formulated from the following ingredients:—

trans 3-trifluoromethyl-*N*-cyclopropylcinnamamide	300 mg
cocoa butter	2000 mg

EXAMPLE 7

A soft gelatin capsule was filled with the following ingredients:—

trans 3-trifluoromethyl-*N*-cyclopropylcinnamamide	300 mg
lactose	75 mg
starch, corn	20 mg
fused silica	2 mg
magnesium stearate	3 mg

EXAMPLE 8

A syrup suspension was prepared from the following ingredients:—

trans 3-trifluoromethyl-*N*-cyclopropylcinnamamide	300 mg
sodium carboxymethylcellulose	20 mg
microcrystalline cellulose	100 mg
glycerin	500 mg
Polysorbate 80	10 ml
flavouring agent	q.s.
preserving agent	0.1%
sucrose syrup	q.s. to 5 ml

EXAMPLE 9

A compressed tablet was prepared from the following:

trans 3-trifluoromethyl-*N*-cyclopropylcinnamamide	300 mg
starch, corn	50 mg
microcrystalline cellulose	50 mg
stearic acid	4 mg
magnesium stearate	1 mg
fused silica	1 mg

EXAMPLE 10

A soft gelatin capsule was filled with the following ingredients:—

trans 3-fluoro-*N*-cyclopropylcinnamamide	300 mg
lactose	75 mg
starch, corn	20 mg
fused silica	2 mg
magnesium stearate	3 mg

EXAMPLE 11

A syrup suspension was prepared from the following ingredients:—

trans 3-bromo-*N*-cyclopropylcinnamamide	300 mg
sodium carboxymethylcellulose	20 mg
microcrystalline cellulose	100 mg
glycerin	500 mg
Polysorbate 80	10 ml
flavoring agent	q.s.
preserving agent	0.1%
sucrose syrup	q.s. to 5 ml

EXAMPLE 12

A syrup suspension was prepared from the following ingredients:—

trans 3-fluoro-*N*-cyclopropylcinnamamide	300 mg
sodium carboxymethylcellulose	20 mg
microcrystalline cellulose	100 mg
glycerin	500 mg
Polysorbate 80	10 ml
flavoring agent	q.s.
preserving agent	0.1%.
sucrose syrup	q.s. to 5 ml

EXAMPLE 13

A compressed tablet was prepared from the following:—

trans 3-bromo-*N*-cyclopropylcinnamamide	300 mg
starch, corn	50 mg
microcrystalline cellulose	50 mg
stearic acid	4 mg
magnesium stearate	1 mg
fused silica	1 mg

EXAMPLE 14

A compressed tablet was prepared from the following ingredients:—

trans 3-fluoro-*N*-cyclopropylcinnamamide	300 mg
starch, corn	50 mg
microcrystalline cellulose	50 mg
stearic acid	4 mg
magnesium stearate	1 mg
fused silica	1 mg

EXAMPLE 15

Anticonvulsant activity

In the MES pharmacological test referred to hereinbefore, the stated compounds had the given ED_{50} when administered i.p. to mice.

Compound	ED_{50} (mg/kg)
trans 3-fluoro-*N*-cyclopropylcinnamamide	60
trans 3-bromo-*N*-cyclopropylcinnamamide	77
trans 3-trifluoromethyl-*N*-cyclopropylcinnamamide	56
trans 3-bromo-*N*-isobutylcinnamamide	46
trans 3-fluorocinnamamide	58

EXAMPLE 16

Muscle relaxant activity

The effect of 3-fluoro-*N*-cyclopropylcinnamamide as a centrally acting muscle relaxant was determined using a method based on that described in Berger, F.M. & Bradley, W. (Br. J. Pharmac. Chemother., (1946), *1*, 265—272) and Crankshaw, D. P. & Raper, C. (Br. J. Pharmac. (1970), *38*, 148—156). At an oral dose of from 100—150 mg/kg the compound suppressed polysynaptic reflex contractions in the cat without affecting the monosynaptic knee-jerk reflex.

EXAMPLE 17

Anticonvulsant activity

When *trans* 3-trifluoromethyl-*N*-cyclopropylcinnamamide was administered to rats according to the MES test it was found to have an ED_{50} of 20±6 mg/kg and 18±3 mg/kg when administered orally and intraperitoneally respectively.

EXAMPLE 18

A solution of *trans* 3-trifluoromethylcinnamoyl chloride (8.5 g) in anhydrous toluene (150 ml) was added to a solution of cyclopropylamine (5 g) in anhydrous toluene (100 ml). The reaction mixture was allowed to stand at room temperature for several hours. The solvent and excess amine were removed under reduced pressure. The residue thoroughly triturated with water and recrystallised from ethanol/water (1/15) to give trans 3-trifluoromethyl-N-cyclopropylcinnamamide m.p. 98°C. Elemental analysis as well as NMR and IR spectra confirmed the structure.

EXAMPLES 19—55

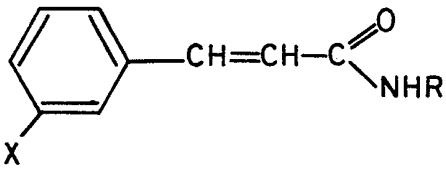
Following the procedure of Example 1, the following *trans* cinnamamide derivatives were prepared (in all cases the NMR, IR and elemental analyses confirmed the structures), which derivatives are compounds of formula (I) having the indicated values for X and R:—

Example	X	R	m.p. °C
19	F	cyclopentyl	138—139
20	F	cyclohexyl	150
21	F	cycloheptyl	152
22	F	cyclooctyl	149—150
23	Cl	cyclopentyl	107—108
24	Cl	cyclohexyl	153—154
25	Cl	cycloheptyl	119—120
26	Cl	cyclooctyl	91—92
27	Br	cyclopentyl	109—110
28	Br	cyclohexyl	158
29	Br	cycloheptyl	101—102
30	Br	cyclohexylmethyl	120—121
31	I	cyclopentyl	126—127
32	CF_3	cyclopentyl	90—92
33	CF_3	cyclohexyl	125
34	CF_3	cycloheptyl	98—100
35	CF_3	cyclooctyl	80
36	CF_3	cyclohexylmethyl	96.5—97.5
37	F	C_2H_5	97
38	F	*iso*-propyl	95—96
39	F	cyclobutyl	105
40	Cl	*iso*-butyl	111.5—112.5
41	Cl	cyclopropyl	112—113
42	Cl	cyclobutyl	99
43	Br	*tert*-butyl	154
44	Br	cyclobutyl	114—115
45	Br	cyclooctyl	101
46	I	*iso*-butyl	109—110
47	I	*tert*-butyl	152—153
48	I	cyclopropyl	123
49	CF_3	H	102
50	CF_3	CH_3	125
51	CF_3	C_2H_5	90
52	CF_3	*n*-propyl	82—83

53	CF_3	*iso*-butyl	116
54	CF_3	*iso*butyl	93
55	CF_3	cyclobutyl	132

WHAT WE CLAIM IS:—

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



(I)

wherein X is fluoro, chloro, bromo, iodo or trifluoromethyl and R is branched alkyl having 4 to 8 carbon atoms, cycloalkyl having 3 to 8 carbon atoms, cycloalkylalkyl wherein the cycloalkyl moiety has 3 to 8 carbon atoms and the alkyl moiety has 1 to 3 carbon atoms and when X is fluoro or trifluoromethyl R may also be hydrogen or alkyl having 1 to 3 carbon atoms, in association with a pharmaceutically acceptable carrier.

2. The composition of claim 1 wherein in formula (I) when X is chloro then R is not branched alkyl having 4 carbon atoms.

3. The composition of claim 1 or 2 wherein in formula (I) R is cycloalkyl having 3 to 6 carbon atoms.

4. The composition of any preceding claim wherein in formula (I) R is cyclopropyl.

5. The composition of any preceeding claim wherein in formula (I) X is fluoro or trifluoromethyl.

6. The composition of any preceeding claim wherein the compound of formula (I) is 3-fluoro-*N*-cyclopropylcinnamamide.

7. The composition of any of claims 1 to 5 wherein the compound of formula (I) is 3-trifluoromethyl-*N*-cyclopropylcinnamamide.

8. The composition of any preceeding claim wherein the compound of formula (I) has the *trans* configuration.

9. The composition of any preceeding claim wherein the carrier is a solid.

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

11. A sterile, injectable composition according to claim 10.

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

13. A composition according to any of claims 1 to 12 in unit-dose form.

14. A composition according to claim 13 which is an orally ingestible tablet.

15. A unit-dose composition according to either of claims 13 and 14 which contains a compound of formula (I) in an amount in the range 100 to 500 mg.

16. A composition according to any of claims 1 to 8 which comprises a suspension of a compound of formula (I) in an orally ingestible liquid carrier.

17. A composition according to any preceding claim substantially as hereinbefore described with particular reference to the Examples.

18. A method for the preparation of a composition according to any of claims 1 to 17 which comprises admixture of the components thereof followed, where appropriate, by disposition of the bulk composition into unit doses thereof.

19. The compound of formula (I) as defined in any of claims 2 to 8.

20. 3-Fluoro-*N*-cyclopropylcinnamamide.

21. 3-Trifluoromethyl-*N*-cyclopropylcinnamamide.

22. 3-Bromo-*N*-cyclopropylcinnamamide.

23. 3-Bromo-*N*-isobutylcinnamamide.

24. 3-Fluorocinnamamide.

25. The *trans* isomer of a compound claimed in any of claims 19 to 24.

26. *trans* 3-Fluoro-*N*-cyclopropylcinnamamide.

27. *trans* 3-Trifluoromethyl-*N*-cyclopropylcinnamamide.

28. A method for the preparation of a compound according to any of claims 19 to 27 which comprises reaction of an amine R . NH_2 with an acid of formula (II); *m*—X—Ph . CH:CH . CO_2H or a reactive derivative thereof, wherein R and X have the meanings defined in formula (I).

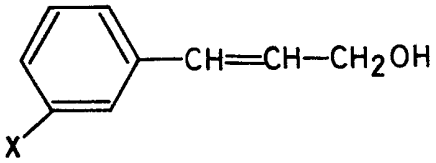
29. A method according to claim 28 wherein the reactive derivative of the acid of formula (II) is selected from an amide, an acid halide, the acid anhydride, and an alkyl ester or alkyl thioester where in each case the alkyl has 1 to 4 carbon atoms.

30. A method according to claim 29 wherein the acid halide is the acid chloride.

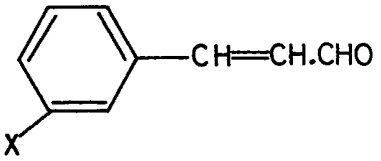
31. A method according to any of claims 28 to 30 for the preparation of *trans* 3-fluoro-*N*-cyclopropylcinnamamide which comprises reaction of *trans* 3-fluorocinnamoyl chloride with cycloproylamine.

32. A method according to any of claims 28 to 30 for the preparation of trans 3-trifluoromethyl-*N*-cyclopropylcinnamamide which comprises reaction of *trans*. 3-trifluoromethylcinnamoyl chloride with cyclopropylamine.

33. A method for the preparation of a compound according to any of claims 19 to 27 which comprises reaction of an amine R . NH_2 with an alcohol or aldehyde of formula (III) or (IV) respectively,



(III)



(IV)

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.

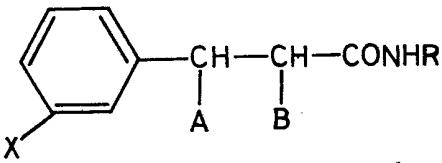
34. A method for the preparation of a compound according to any of claims 19 to 27 which comprises reaction of a compound of formula (V): R . NH . W with an acid of formula (II): *m*—X—Ph . CH: CH . CO_2H or a reactive derivative thereof, wherein R and X have the meanings defined in formula (I) and W is a leaving group.

35. A method according to claim 34 wherein the leaving group W is selected from —CO . H, —$CONH_2$, —CONHR wherein R has same meaning as in formula (I), —CO . Alk, —COOAlk wherein each Alk represents alkyl having from one to four carbon atoms.

36. A method according to either of claims 34 and 35 wherein the reactive derivative of the acid of formula (II) is selected from the acid anhydride and an acid halide.

37. A method according to claim 36 wherein the acid halide is the acid chloride.

38. A method for the preparation of a compound according to any of claims 19 to 27 which comprises elimination of the elements of water, a hydrogen halide or molecular halogen, as appropriate, from a compound of formula (VI):



(VI)

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

39. A method according to claim 38 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.

40. A method according to claim 38 wherein one of A and B is halo and the other is hydrogen and the compound of formula (VI) is treated with a base or is heated.

41. A method according to claim 38 wherein A and B are the same and each is halo and the compound of formula (VI) is treated with a suitable reducing agent.

42. A method of preparing a compound of formula (I) as defined in any of claims 19 to 27 substantially as hereinbefore described with particular reference to the Examples.

43. A compound of formula (I) as defined in any one of claims 19 to 27 when prepared by a method claimed in any one of claims 28 to 42.

44. A method for the treatment or prophylaxis of convulsions of a mammal excluding man comprising administration to said mammal of a non-toxic, effective anti-convulsant amount of a compound of formula (I) as defined in any one of claims 1 to 8 and 19 to 27.

45. The method as claimed in claim 44 wherein the convulsions are associated with grand mal, petit mal, psychomotor epilepsy or focal seizures.

46. The method as claimed in claim 44 or 45, wherein the compound is *trans* 3-trifluoromethyl-*N*-cyclopropylcinnamamide.

47. A method of decreasing tone in skeletal muscles of a mammal excluding man which comprises administration to said mammal of a non-toxic effective tone decreasing amount of a compound of formula (I) as defined in any one of claims 1 to 8 and 19 to 27.

48. The method of claim 47 for the treatment of parkinsonism, chorea, arthritis, athetosis, status epilepticus, tetanus, myositis, spondylitis, cerebral palsy or multiple sclerosis.

49. The method as claimed in claim 47 or 48 wherein the compound of formula (I) is *trans* 3-fluoro-*N*-cyclopropylcinnamamide.

50. The method according to any one of claims 44 to 49 wherein the compound is administered by the oral route.

51. The method according to any of claims 44 to 50 wherein the compound is administered at a dose of from 2 to 200 mg/kg mammal bodyweight per day.

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