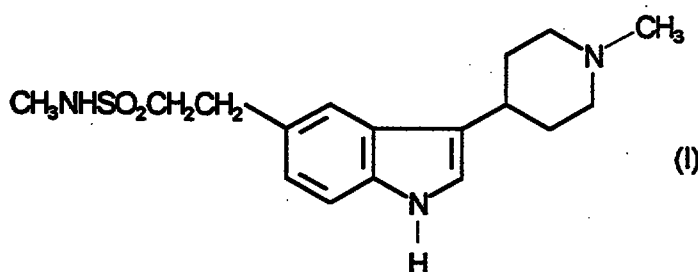


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**PROCESS**

This invention relates to a process for the preparation of N-methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulphonamide and physiologically acceptable salts and solvates thereof.

N-Methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulphonamide, which may be represented by the formula (I)

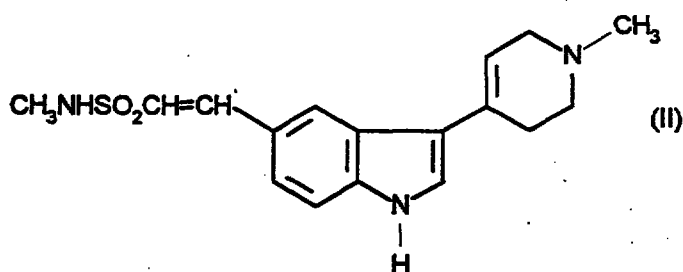


and its physiologically acceptable salts and solvates are disclosed in GB2208646. It exhibits selective vasoconstrictor activity and is indicated for use in the treatment of migraine.

GB2208646 describes inter alia a process for preparing the compounds disclosed therein which comprises reducing the appropriate 3-(1,2,3,6-tetrahydro-1-methyl-4-pyridiny)-indole-5-ethanesulphonamide derivative and a process which comprises reducing the appropriate 3-(1-methyl-4-piperidiny)-indole-5-ethanesulphonamide derivative. However, there is no specific disclosure of a process which comprises reducing a 3-(1,2,3,6-tetrahydro-1-methyl-4-pyridiny)-indole-5-ethanesulphonamide derivative.

We have now surprisingly found that the compound of formula (I) can be prepared in good yield and high purity by reduction of a novel diene intermediate.

Thus, the present invention provides a process for preparing compound (I) or a salt thereof which comprises reducing the compound of formula (II)



or a salt thereof.

The reduction process may conveniently be carried out in the presence of hydrogen and a noble metal catalyst such as palladium, palladium oxide, Raney nickel, platinum, platinum oxide or rhodium which may be supported, for example, on charcoal e.g. 10% palladium oxide on charcoal. Alternatively a homogenous catalyst such as tris(triphenylphosphine) rhodium chloride may be used. The reduction may be carried out in a suitable solvent or combination of solvents such as water, alcohol e.g. methanol or ethanol, ether e.g. dioxan, ester e.g. ethyl acetate or amide e.g. dimethylformamide, conveniently at a temperature of 10 to 50°C. Alternatively, the reduction may be carried out under conditions for catalytic hydrogen transfer using, for example, palladium in the presence of a hydrogen donor such as formic acid or its salts.

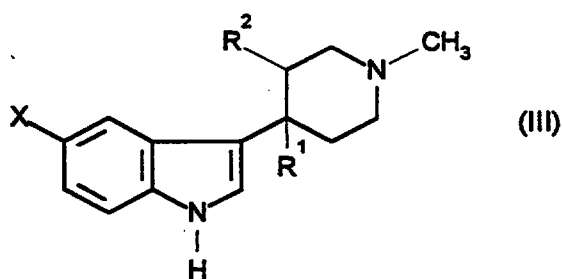
In a particularly preferred embodiment of the invention the reduction process is catalysed by 10% palladium oxide on charcoal advantageously added to the reaction vessel in the form of a wet paste e.g. 50% (w/w).

The intermediate of formula (II) and salts thereof are novel compounds and represent a further aspect of the invention.

Accordingly the invention provides N-methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethanesulphonamide and salts thereof for use as intermediates.

Suitable salts include acid addition salts formed with organic or inorganic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, fumarates, maleates, creatine sulphates and methanesulphonates.

The compound of formula (II) or a protected derivative or a salt thereof may be prepared by condensing a compound of formula (III)



or a salt thereof, wherein R^1 is a hydroxy group and R^2 is hydrogen or R^1 and R^2 together form a double bond, X represents a leaving atom such as a halogen atom, for example a bromine atom, or a leaving group, for example a triflate (CF_3SO_3) group, with an N-methyl vinylsulphonamide of formula (IV)



where Z is hydrogen or an amino protecting group, and optionally, if necessary and/or desired, deprotecting a protected derivative so obtained.

Typical amino protecting groups are well known to those skilled in the art and may be used in conventional manner. See, for example, "Protective Groups in Organic Chemistry", Ed. J.F.W. McOmie (Plenum Press 1973) or "Protective Groups in Organic Synthesis" by T.W. Greene (John Wiley & Sons 1981). Thus, for example, amino protecting groups include tertiary butyl, silyl, for example trimethylsilyl, aralkyl groups and acyl groups. Removal of such groups may be achieved by conventional procedures.

The reaction will generally be effected in the presence of a palladium catalyst such as, for example palladium or palladium oxide on charcoal or a palladium salt or complex. Palladium salts which may be employed as catalysts include salts of organic acids such as acetates or salts of inorganic acids such as chlorides or bromides. Palladium complexes include, for example, lithium tetrachloropalladate and zero valent complexes such as bis(dibenzylideneacetone)palladium and tetrakis(triphenylphosphine)palladium. Palladium acetate is a preferred catalyst.

Optionally, the reaction may be effected in the presence of a base, for example, a tertiary nitrogen base such as triethylamine or tri-n-butylamine, alkali metal carbonate such as sodium carbonate, alkali metal hydrogen carbonate such as sodium hydrogen carbonate, or an alkali metal acetate such as potassium acetate, optionally together with a phase transfer catalyst such as tetrabutylammonium chloride.

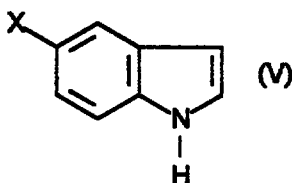


The reaction may optionally be carried out in the presence of a phosphine, for example a triarylphosphine such as triphenylphosphine or tri-*o*-tolylphosphine or a phosphinated polystyrene or bidentate ligand such as diphenylphosphine - $(\text{CH}_2)_x$ -diphenylphosphine where x is an integer of 2,3 or 4. A phosphine should be present when the process is effected with a compound of formula (III) wherein X represents a bromine atom.

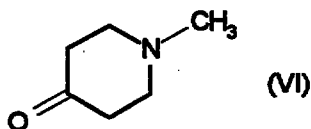
The reaction may be effected in the presence or absence of solvent. An anhydrous or aqueous medium comprising one or more solvents may be employed. Suitable solvents include nitriles, for example acetonitrile, alcohols, for example methanol, amides, for example dimethylformamide or dimethylacetamide, 1-methyl-2-pyrrolidinone or hexamethylphosphoramide, or water. The reaction may conveniently be carried out at a temperature of 25 to 200°C, preferably 75 to 150°C, for example 80 to 110°C.

Certain compounds of formula (III) are known and their preparation is described in GB2208646.

Thus, for example compounds of formula (III) may be prepared by condensing a compound of formula (V)



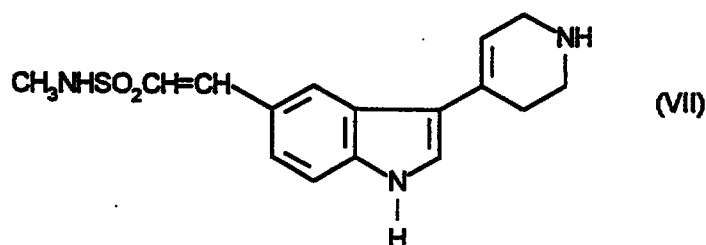
with the piperidone of formula (VI)



in a suitable reaction medium in the presence of an acid or a base, conveniently at a temperature of 0 to 120°C. Compounds of formula (III) wherein R^1 and R^2 together form a double bond are preferably prepared in the presence of a base such as potassium hydroxide at an elevated temperature, for example at the reflux temperature of the reaction mixture. In contrast, compounds of formula (III) wherein R^1 is a hydroxy group and R^2 is hydrogen are preferably prepared in the presence of a base such as potassium hydroxide at room temperature. The reaction may conveniently be carried out in a suitable solvent such as an alcohol, for example methanol or ethanol.



Alternatively the compound of formula (II) may be prepared by methylating the compound of formula (VII)

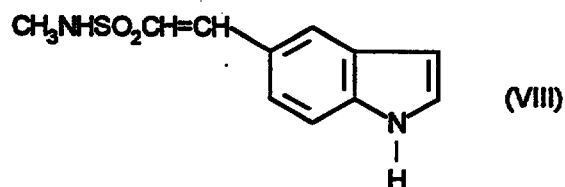


using conventional techniques.

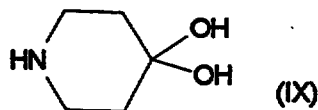
5 Thus, for example, the compound of formula (II) may be prepared by methylating the compound of formula (VII) by reductive amination using aqueous formaldehyde and sodium borohydride in a suitable solvent such as methanol or using aqueous formaldehyde and formic acid at 100°C (Eschweiler-Clarke conditions).

10 Alternatively, the reaction may be effected using a suitable methylating agent such as a methyl halide, methyl tosylate or dimethylsulphate. The methylation may conveniently be carried out in an inert organic solvent such as an amide, for example dimethylformamide, an ether, for example tetrahydrofuran, an alcohol, for example methanol or industrial methylated spirits, or a nitrile, for example acetonitrile, preferably in the presence of a base. Suitable bases include, for example, alkali metal carbonates such as sodium carbonate, or alkali metal hydrogen carbonates such as sodium or potassium hydrogen carbonate. The methylation reaction is conveniently carried out at a temperature of 25 to 100°C.

20 The compound of formula (VII) may be prepared by reaction of the compound of formula (VIII)



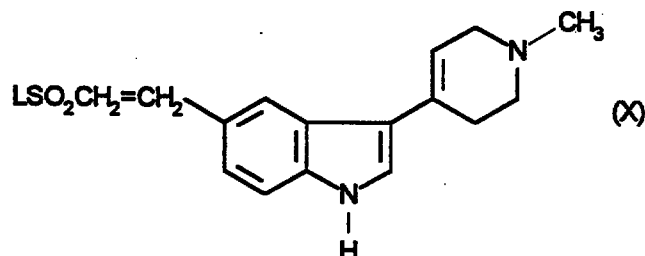
with the compound of formula (IX)





using appropriate conditions as described above for the preparation of compounds of formula (III) from compounds of formula (V) and (VI).

Alternatively, the compound of formula (II) may be prepared by condensing a compound of formula (X)



wherein L is a suitable leaving group, with methylamine. Suitable leaving groups include, for example, halogen atoms such as chlorine and aryloxy groups such as phenoxy.

The condensation process may be effected in a suitable reaction medium such as an amide e.g. dimethylformamide, an ether e.g. tetrahydrofuran, a nitrile e.g. acetonitrile, a haloalkane e.g. dichloromethane, or mixtures thereof, optionally in the presence of an organic base such as pyridine or triethylamine or an inorganic base such as calcium carbonate or sodium bicarbonate. Conveniently the reaction is effected at a temperature of -70 to 150°C.

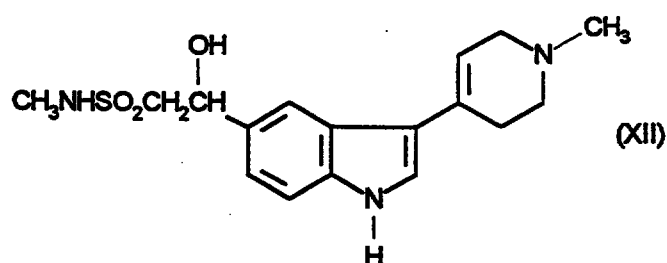
Compounds of formula (X) may be prepared by reaction of a compound of formula (III) wherein R¹ and R² together form a double bond with a compound of formula (XI)



wherein Y is a leaving group L as defined above or a group susceptible to replacement by a leaving group L, for example a hydroxy group, using appropriate conditions as described above for the preparation of the compound of formula (II) from compounds of formula (III) and (IV).

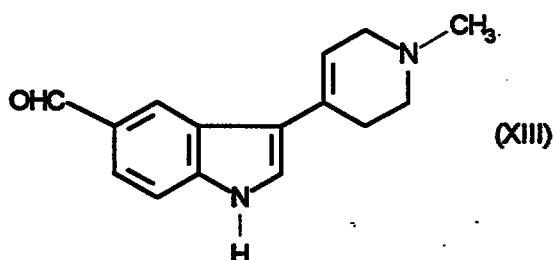
Thus, for example, a compound of formula (X) may be prepared by reaction of a compound of formula (III) wherein R¹ and R² together form a double bond with a compound of formula (XI) wherein Y is a hydroxy group, followed by reaction with a halogenating agent such as PCl₅ or SOCl₂ using conventional techniques.

Alternatively, the compound of formula (II) may be prepared by dehydrating the compound of formula (XII)



in the presence of an acid or a base.

The compound of formula (XII) may be prepared by reaction of the compound of formula (XIII)

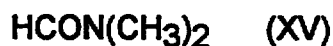


with the compound of formula (XIV)



in the presence of a strong base such as n-butyl lithium.

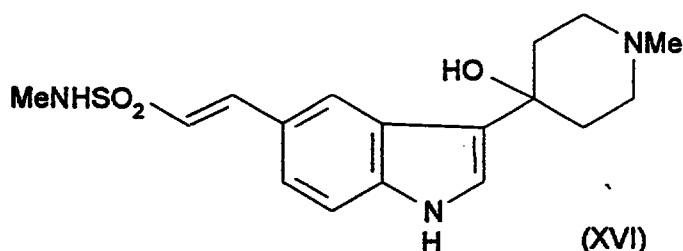
The compound of formula (XIII) may be prepared by reaction of a compound of formula (III) wherein R^1 and R^2 together form a double bond with the compound of formula (XV)



in the presence of an alkyl lithium reagent.

Alternatively the compound of formula (II) may be prepared by reacting the compound of formula (VIII) with the compound of formula (VI) using appropriate conditions as described above for the preparation of compounds of formula (III) from compounds of formula (V) and (VI).

Alternatively the compound of formula (II) may be prepared by dehydrating the compound of formula (XVI)



for example in the presence of an acid or a base such as potassium hydroxide.

The compound of formula (XVI) may be prepared by reaction of the compound of formula (VIII) with the compound of formula (VI) using appropriate conditions as described above for the preparation of compounds of formula (III) wherein R¹ is a hydroxy group and R² is hydrogen from compounds of formula (V) and (VI).

Where it is desired to isolate compound (I) as a physiologically acceptable salt, this may be formed by conventional methods, for example by treatment with an appropriate acid in a suitable solvent. Solvates of compound (I) may conveniently be prepared by crystallisation or recrystallisation from an appropriate solvent.

The invention is further illustrated by the following non-limiting examples. All temperatures are in °C. IMS means industrial methylated spirit. DMF means N-N-dimethylformamide.

Intermediate 1

5-Bromo-3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indole

Process A

A mixture of 5-bromoindole (1kg), 1-methyl-4-piperidone (692mL) and potassium hydroxide (30.6g) in IMS (6.0L) was heated under reflux under nitrogen for 18hr. The suspension was cooled to 5-10°, aged for 15min and filtered. The filter cake was washed with methanol (300mL) followed by water (800mL) then dried in vacuo at 50°. The product was obtained as a white solid (1.40kg, 94% of theory).

NMR:- 2.31 δ (3H) s; 2.54 δ (2H+DMSO-d₅) m; 2.61 δ (2H) m; 3.08 δ (2H) m; 6.12 δ (1H) m; 7.27 δ (1H) d of d, J = 8.5Hz, 1.9Hz; 7.40 δ (1H) d, J = 8.5Hz; 7.50 δ (1H) s; 7.98 δ (1H) d, J = 1.9Hz; 11.4 δ (1H) broad s.

Process B

A mixture of 5-bromoindole (5.0g), 4-dihydroxy-1-methylpiperidine hydrochloride (5.72g) and potassium hydroxide (2.28g) in 1-propanol (45mL) was heated



under reflux under nitrogen for 5h. The suspension was cooled to ambient temperature and filtered. The filter cake was washed with 1-propanol (2 x 5mL) followed by water (2 x 10mL) then dried *in vacuo* at 50° overnight. The product was obtained as a white solid (5.7g, 76% of theory).

5 NMR:- 2.32 δ (3H) s; 2.54 δ (2H+DMSO- d_5) m; 2.61 δ (2H) m; 3.08 δ (2H) m; 6.11 δ (1H) m; 7.27 δ (1H) d of d, J = 8.5Hz, 1.9Hz; 7.40 δ (1H) d, J = 8.5Hz; 7.49 δ (1H) s; 7.96 δ (1H) d, J = 1.9Hz; 11.4 δ (1H) broad s.

Intermediate 2

10 5-Bromo-3-(4-hydroxy-1-methyl-4-piperidiny)-1H-indole

A mixture of 5-bromoindole (490g), 1-methyl-4-piperidone (339mL) and potassium hydroxide (15g) in IMS (3L) was stirred under nitrogen at room temperature for 24hrs. The mixture was cooled to 7° and filtered. The filter cake was washed with ethanol (300mL) followed by water (800mL) to give an off-white powder which was dried *in vacuo* at 50° for 24hr (563.8g, 73% of theory).

15 NMR:- 1.89 δ (2H) m; 2.03 δ (2H) m; 2.24 δ (3H) s; 2.55 δ (obscured by DMSO- d_5) m; 4.70 δ (1H) s; 7.19 δ (1H) d of d, J = 8.7Hz, 2.0Hz; 7.24 δ (1H) d, J = 2.3Hz; 7.35 δ (1H) d, J = 8.7Hz; 7.98 δ (1H) d, J = 2.0Hz; 11.08 δ (1H) broad s.

20

Intermediate 3

(E)-N-Methyl-2-(1H-indol-5-yl)ethenesulphonamide.

25 A mixture of N-methylethanesulphonamide (45g), 5-bromoindole (60g), palladium acetate (0.9g), tri-*o*-tolylphosphine (18.6g) and triethylamine (90mL) in isopropanol (300mL) was heated at 85° under nitrogen for 18h. The reaction mixture was cooled to ambient temperature, filtered and the filter cake washed with isopropanol (30mL). The combined washings and filtrate were concentrated *in vacuo* to give a yellow-brown solid (160g). This material was purified by column chromatography on silica gel. Eluting initially with ethyl acetate/cyclohexane (1:1) followed by ethyl acetate provided the product (26.4g, 36% of theory) as a yellow powder.

30

NMR:- 2.55 δ (3H) d, J = 4.9Hz; 6.51 δ (1H) m; 6.97 δ (1H) d, J = 15.5Hz; 7.00 δ (1H) m; 7.43 δ (1H) d, J = 15.5Hz; 7.42 δ (1H) d, J = 2.8Hz; 7.45 δ (1H) d, J = 8.6Hz; 7.49 δ (1H) d of d, J = 8.6, 1.5Hz; 7.90 δ (1H) s; 11.35 δ (1H) broad s.

Intermediate 4(E)-N-Methyl-2-[3-(4-hydroxy-1-methyl-4-piperidiny)-1H-indol-5-yl]ethenesulphonamide

5 A mixture of (E)-N-methyl-2-(1H-indole-5-yl)ethenesulphonamide (2.0g), 1-methyl-4-piperidone (1.62g) and potassium hydroxide (0.7g) in IMS (20mL) was stirred at ambient temperature for 22hr. The reaction mixture was concentrated and the residue purified by column chromatography on silica gel. Eluting with dichloromethane/ethanol/ammonia (25:10:1) gave an oil which solidified on
10 standing to a brown solid. Trituration with ether provided the product as a white powder (1.85g, 64% of theory).

NMR:- 1.94 δ (2H) m; 2.10 δ (2H) m; 2.24 δ (3H) s; 2.46 δ (2H) m; 2.55 δ (2H+DMSO-d₅) m; 4.69 δ (1H) broad s; 6.93 δ (1H) d, J=15.4Hz; 7.00 δ (1H) broad s; 7.25 δ (1H) d, J=1.7Hz; 7.42 δ (1H) d, J=8.5Hz; 7.45 δ (1H) d, J=15.4Hz; 7.49 δ (1H) d of d, J=8.5, 1.7Hz; 11.12 δ (1H) broad s.
15

Example 1(E)-N-Methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethenesulphonamide

20 A mixture of N-methylethanesulphonamide (460g), Intermediate 1 (1kg), palladium acetate (15.4g), tri-*o*-tolylphosphine (315g), triethylamine (960mL) and celite (400g) in DMF (5L) was heated between 100-108° under nitrogen for 2½hr. The suspension was cooled to 5°, filtered and the filter cake washed with DMF (2L). A portion (3.7L) of the filtrate was stirred with water (250mL) and
25 cyclohexane (3.0L) for 10min. The phases were separated and the DMF layer re-extracted with cyclohexane (1x3.0L, 1x1.5L). The DMF solution was heated to 90° and water (2L) added over 40min. The mixture was cooled to 10° over 3hr and then aged at 5° for 14hr. The solid obtained was filtered off, washed with cold (10°) DMF/water (2:1) (2x500mL) and dried in vacuo at 50° for 18hr to
30 afford a yellow powder (323.2g, 60% of theory).

NMR:- 2.33 δ (3H) s; 2.55 δ m; 2.57 δ broad s; 2.60 δ m (7H + DMSO-d₅); 3.10 δ (2H) m; 6.30 δ (1H) m; 7.00 δ (1H) broad resonance; 7.05 δ (1H) d, J = 15.7Hz; 7.45 δ (1H) d, J = 8.4Hz; 7.47 δ (1H) broad s; 7.51 δ (1H) d, J = 15.7Hz; 7.54 δ (1H) d of d, J = 8.4Hz, 1.6Hz; 8.17 δ (1H) broad s; 11.38 δ (1H) broad s.
35

Example 2(E)-N-Methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethanesulphonamide

5 A mixture of N-methylethanesulphonamide (460g), Intermediate 1 (1kg), palladium acetate (15.4g), tri-*o*-tolylphosphine (315g), triethylamine (960mL) and celite (400g) in DMF (5L) was heated between 100-108° under nitrogen for 2½hr. The suspension was cooled to 5°, filtered and the filter cake washed with DMF (2L). Water (2.5L) was added dropwise to a cold (4°) portion (3.7L) of the filtrate. The suspension was cooled to 5°, aged for 45min and filtered. The filter cake was washed with cold DMF/water (7:5) (1L) followed by cold IMS (1L). The residue was slurried with ethyl acetate (2.76L) at room temperature for 1hr then filtered. The filter cake was washed with ethyl acetate (500mL) and the collected solid dried overnight in vacuo at 45° (394.6g, 69.3% of theory).

15 NMR:- 2.32 δ (3H) s; 2.55 δ m; 2.56 δ d (J = 4.8Hz); 2.60 δ m (7H + DMSO-d₅); 3.09 δ (2H) m; 6.29 δ (1H) m; 6.99 δ (1H) q, J = 4.8Hz; 7.04 δ (1H) d, J = 15.7Hz; 7.44 δ (1H) d, J = 8.4Hz; 7.46 δ (1H) broad s; 7.51 δ (1H) d, J = 15.7Hz; 7.54 δ (1H) d of d, J = 8.4Hz, 1.6Hz; 8.17 δ (1H) broad s; 11.38 δ (1H) broad s.

Example 3(E)-N-Methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethanesulphonamide

20 A mixture of N-methylethanesulphonamide (15.74g), Intermediate 1 (30.02g), palladium acetate (2.08g), tri-*o*-tolylphosphine (7.21g) and triethylamine (28.7mL) in DMF (90mL) was heated to 110-115° for 4hr. The mixture was filtered, whilst still hot, through hyflo. The filtrate was cooled to 0-5° and ice cold water (300ml) added over 30mins. The mixture was stirred at 0-5° for 1¼hr then aged at 5° overnight. The resulting solid was collected by filtration washed with water (90mL) and sucked dry for 20min. The yellow solid was slurried with ethyl acetate (120mL) at room temperature for 3hr. The product was filtered off, washed with ethyl acetate (30mL) and dried in vacuo at 55° overnight (28.06g, 82% of theory).

30 NMR:- 2.31 δ (3H) s; 2.55 δ m; 2.56 δ d (J = 4.8Hz); 2.60 δ m (7H + DMSO-d₅); 3.08 δ (2H) m; 6.28 δ (1H) m; 6.98 δ (1H) q, J = 4.8Hz; 7.03 δ (1H) d, J = 15.7Hz; 7.43 δ (1H) d, J = 8.4Hz; 7.45 δ (1H) d, J = 1.9Hz; 7.49 δ (1H) d, J = 15.7Hz; 7.52 δ (1H) d of d, J = 8.4Hz, 1.6Hz; 8.16 δ (1H) broad s; 11.38 δ (1H) broad s.

Example 4(E)-N-Methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethenesulphonamide, hydrochloride

5 A mixture of N-methylethanesulphonamide (320g), Intermediate 1 (700g), palladium acetate (10.5g), tri-*o*-tolylphosphine (140g), triethylamine (670mL) and celite (280g) in DMF (3.5L) was heated at 85° for 4hr. The mixture was filtered, whilst hot, and the filter cake washed with DMF (700mL). The filtrate was cooled to 15-20° and water (8.4L) added dropwise. The mixture was aged at 8°, filtered, the product washed with water (2.1L) then dried in vacuo overnight at 40°. The crude product was slurried in ethyl acetate (2.8L) at 21°C for 3hr. The suspension was collected by filtration and washed with ethyl acetate (700mL). The wet cake was suspended in DMF (2.1L), cooled to 15° whereupon concentrated hydrochloric acid (210mL) was added over 30min at <25°. Ethyl acetate (1.4L) was added dropwise over 30mins. After a further 30mins more ethyl acetate (5.6L) was introduced over 1hr. The product was filtered off, washed with ethyl acetate (1.4L) followed by 2-propan-1-ol (700mL) and dried in vacuo at 45° overnight (791.5g, 89.5% of theory).

20 NMR:- 2.55 δ (3H) d, J = 5.0Hz; 2.82 δ (2H) broad m; 2.89 δ (3H) s; 3.30 δ (1H) broad m; 3.58 δ (1H) broad m; 3.79 δ (1H) broad m; 3.98 δ (1H) broad m; 6.34 δ (1H) m; 7.05 δ (1H) q, J = 5.0Hz; 7.07 δ (1H) d, J = 15.4Hz; 7.47 δ (1H) d, J = 8.5Hz; 7.50 δ (1H) d, J = 15.4Hz; 7.58 δ (1H) d of d, J = 8.5Hz, 1.3Hz; 7.62 δ (1H) d, J = 2.6Hz; 8.22 δ (1H) broad s; 10.7 δ (1H) broad resonance; 11.68 δ (1H) broad s.

25

Example 5(E)-N-Methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethenesulphonamide

30 A stirred mixture of Intermediate 2 (30.08g), N-methylethanesulphonamide (14.84g), palladium acetate (1.97g), tri-*o*-tolylphosphine (6.81g) and triethylamine (27mL) in DMF (90mL) was heated at 110-115° for 4hr. The hot (90°) mixture was filtered and the residue washed with DMF (30mL). Water (300mL) was added dropwise to the filtrate which was then cooled to 5° and aged for 30mins. The suspension was filtered, washed with water (3x30mL) and sucked dry for 1½hr. The damp cake was slurried with ethyl acetate (120mL) for

35



3hr, filtered and the residue washed with ethyl acetate (30mL). The product was dried *in vacuo* at 55° for 18hr (27.52g, 85% of theory).

NMR:- 2.31 δ (3H) s; 2.55 δ m; 2.56 δ d, J = 4.8Hz; 2.60 δ m, (7H + DMSO- d_5); 3.08 δ (2H) m; 6.28 δ (1H) m; 6.98 δ (1H) q, J = 4.8Hz; 7.03 δ (1H) d, J = 15.7Hz; 7.43 δ (1H) d, J = 8.4Hz; 7.45 δ (1H) d, J = 1.9Hz; 7.50 δ (1H) d, J = 15.7Hz; 7.53 δ (1H) d of d, J = 8.4Hz, 1.6Hz; 8.16 δ (1H) broad s; 11.39 δ (1H) broad s.

Example 6

(E)-N-Methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethenesulphonamide

A mixture of N-methylethanesulphonamide (115g), Intermediate 1 (250g), palladium acetate (3.85g), tri-*o*-tolylphosphine (77.5g), triethylamine (240mL) and celite (100g) in DMF (1.25L) was heated between 100-110° under nitrogen for 2h. The suspension was cooled to 20°, filtered and the filter cake washed with DMF (500mL). The combined washings and filtrate were stirred with water (125mL) and cyclohexane (1.5L). The phases were separated and the DMF layer re-extracted with cyclohexane (1 x 1.5L, 1 x 0.75L). The DMF solution was treated with triethylamine (125mL). Water (1.0L) was added at $\leq 35^\circ$ over 20min. The suspension was cooled to 5° over 30min and aged for 1.5h. The solid was filtered off, washed with DMF/water (2:1) (2 x 250mL) followed by water (125mL) and dried *in vacuo* at 50° for 18h to afford a yellow powder (194.3g, 69% of theory).

NMR:- 2.33 δ (3H) s; 2.5 δ m, 2.56 δ broad s, 2.61 δ m (7H + DMSO - d_5); 3.10 δ (2H) m; 6.30 δ (1H) m; 7.08 (1H) broad resonance, 7.04 δ (1H) d, J = 15.7Hz; 7.44 δ (1H) d, J = 8.4Hz; 7.46 δ (1H) s, 7.47 δ (1H) d, J = 15.7Hz; 7.54 δ (1H) d of d, J = 8.4Hz, 1.6Hz; 8.18 δ (1H) broad s; 11.4 δ (1H) broad s.

Example 7

(E)-N-Methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethanesulphonamide

A solution of Intermediate 1 (100g) and N-methylethanesulphonamide (46g) in DMF (300mL) and 5N hydrochloric acid (70mL) was added over 0.75h to a stirred mixture of tri-*o*-tolylphosphine (31.3g), palladium acetate (1.54g), celite (40g) and triethylamine (144mL) in DMF (200mL) at 100° under nitrogen. The



reaction was stirred for a further 4h at 100°, cooled to ambient temperature, filtered and the filter cake washed with DMF (2 x 100mL). The combined washings and filtrate were stirred with water (50mL) and cyclohexane (600mL). The phases were separated and the DMF layer re-extracted with cyclohexane (1 x 600mL, 1 x 300mL). The DMF solution was treated with triethylamine (48mL). Water (400mL) was added at ≤35° over 15min, the suspension cooled to 5° and aged for 1h. The solid was filtered off, washed with DMF/water (2:1) (2 x 100mL) and dried *in vacuo* at 50° overnight to afford a yellow powder (76.9g, 68% of theory).

NMR:- 2.32 δ (3H) s; 2.55 δ m, 2.56 δ d (J = 4.8Hz), 2.60 δ m (7H + DMSO - d₅); 3.09 δ (2H) m; 6.28 δ (1H) m; 6.98 δ (1H) q, J = 4.8Hz; 7.03 δ (1H) d, J = 15.7Hz; 7.43 δ (1H) d, J = 8.4Hz; 7.45 δ (1H) s; 7.47 δ (1H) d, J = 15.7Hz; 7.53 δ (1H) d of d, J = 8.4Hz, 1.6Hz; 8.17 δ (1H) broad s; 11.4 δ (1H) broad s.

Example 8

(E)-N-Methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethenesulphonamide

A mixture of N-methylethenesulphonamide (43.08g), Intermediate 2 (100g), palladium acetate (1.45g), tri-*o*-tolylphosphine (29.5g), triethylamine (90mL) and celite (40g) in DMF (500mL) was heated between 100-110° under nitrogen for 4h. The suspension was cooled to 20°, filtered and the filter cake washed with DMF (200mL). The combined washings and filtrate were stirred with water (50mL) and cyclohexane (600mL). The phases were separated and the DMF layer re-extracted with cyclohexane (1 x 600mL, 1 x 300mL). The DMF solution was treated with triethylamine (45mL). Water (400mL) was added at ≤35° over 15min, the suspension cooled to 5° over 1.5h and aged for 1h. The solid was filtered off, washed with DMF/water (2:1) (2 x 100mL) followed by water (50mL) and dried *in vacuo* at 50° for 18h to afford a yellow powder (76.7g, 67% of theory).

NMR:- 2.33 δ (3H) s; 2.55 δ m, 2.57 δ s, 2.62 δ m, (7H + DMSO - d₅); 3.10 δ (2H) m; 6.30 δ (1H) m; 7.0 δ (1H) broad resonance, 7.05 δ (1H) d, J = 15.7; 7.44 δ (1H) d, J = 8.4Hz; 7.46 δ (1H) s; 7.48 δ (1H) d, J = 15.7 Hz; 7.55 δ (1H) d, J = 8.4Hz; 8.18 δ (1H) broad s; 11.4 δ (1H) broad s.

Example 9(E)-N-Methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethenesulphonamide

5 A mixture of Intermediate 3 (3.93g), 1-methyl-4-piperidone (3.42g) and potassium hydroxide (1.41g) in IMS (35mL) was heated under reflux for 17h. The suspension was cooled to ambient temperature and filtered. The filter cake was washed with IMS (5mL) followed by water (10mL) and IMS (5mL) again, then dried *in vacuo*. The crude product was triturated with water (30mL),
10 filtered, the filter cake washed with water (10mL) and dried *in vacuo* at 50° to provide a pale yellow solid (2.30g, 42% of theory).

15 NMR:- 2.35 δ (3H) s; 2.57 δ (2H + DMSO- d_5) m; 2.60 δ (3H) s; 2.64 δ (2H) m; 3.12 (2H) m; 6.32 δ (1H) m; 7.07 δ (1H) d, J = 15.7Hz; 7.47 δ (1H) d, J = 8.4Hz; 7.49 δ (1H) s; 7.53 δ (1H) d, J = 15.7Hz; 7.56 δ (1H) d of d, J = 8.4, 1.6Hz; 8.20 δ (1H) s.

Example 10(E)-N-Methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethene-sulphonamide

20 A mixture of Intermediate 4 (1.0g) and potassium hydroxide (90mg) in IMS (15mL) was heated under reflux for 20hr. The solution was cooled to ambient temperature and the resulting yellow precipitate filtered off. The residue was washed with water (3x5mL) followed by IMS (2x2mL) and dried *in vacuo* to give a yellow powder (0.16g, 17% of theory).

25 NMR:- 2.35 δ (3H) s; 2.57 δ (2H+DMSO- d_5) m; 2.59 δ (3H) s; 2.64 δ (2H) m; 3.12 δ (2H) m; 6.22 δ (1H) m; 7.02 δ (1H) broad resonance; 7.07 δ (1H) d, J=15.7Hz; 7.47 δ (1H) d, J=8.4Hz; 7.49 δ (1H) s; 7.50 δ (1H) d, J=15.7Hz; 7.57 δ (1H) d of d, J=8.4, 1.6Hz; 8.20 δ (1H) s.

Example 11N-Methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide, hydrochloride

30 A mixture of (E)-N-methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethenesulphonamide (10kg) and 10% palladium oxide on charcoal
35 (10kg, 50% wet paste, added as two charges) in DMF (50L), water (20L) and 2N



hydrochloric acid (15L) was hydrogenated at atmospheric pressure over 18.5hr. The catalyst was removed by filtration. The filter cake was washed with water (20L). The filtrate was concentrated in vacuo to approximately 30L and cooled to 20°. Ethyl acetate (70L) was added over 1hr and the resulting suspension cooled to 5° and aged for 30min. The product was collected by filtration, washed with ethyl acetate (20L) and dried in vacuo at 40-50° overnight (9.34kg, 81.6% of theory). A portion (2.0kg) of the solid was recrystallised from hot water (6.0L) and obtained as white crystals (1.40kg, 70% of theory).

NMR:- 2.1 δ (4H) m; 2.64 δ (3H) d, J = 4.9Hz; 2.78 δ (3H) s; 3.04 δ m; 3.11 δ broad m, (5H); 3.33 δ (2H) m; 3.47 δ (2H) m; 7.02 δ (2H) m; 7.14 δ (1H) broad s; 7.31 δ (1H) d, J = 8.2Hz; 7.60 δ (1H) broad s; 10.75 δ (1H) broad resonance; 10.9 δ (1H) broad s.

Example 12

N-Methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulphonamide, hydrochloride

A mixture of (E)-N-methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethanesulphonamide hydrochloride (500g) and 10% palladium oxide on charcoal (50% wet paste, 700g added as three charges) in DMF (3L), water (3L) and methanol (1.5L) was hydrogenated at atmospheric pressure over 24hr. The suspension was filtered and the filter cake washed with water (500mL). The filtrate was concentrated to approximately 2L by distillation in vacuo. Ethyl acetate (5L) was added over 10mins and the mixture cooled to 5°. The product was filtered off, washed with ethyl acetate (1L) and dried in vacuo at 45° overnight (453g, 90.1% of theory). Recrystallisation from hot water (1.36L) afforded white crystals (324.0g, 71.2% of theory).

NMR:- 2.1 δ (4H) m; 2.64 δ (3H) d, J = 4.9Hz; 2.79 δ (3H) s; 3.04 δ m; 3.11 δ broad m, (5H); 3.33 δ (2H) m; 3.47 δ (2H) m; 7.02 δ (2H) m; 7.14 δ (1H) broad s; 7.31 δ (1H) d, J = 8.2Hz; 7.60 δ (1H) broad s; 10.65 δ (1H) broad resonance; 10.9 δ (1H) broad s.

Example 13N-Methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide,
hydrochloride

5 A solution of (E)-N-methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethenesulphonamide (25g) in water (244.5mL) containing methanesulphonic acid (5.5mL) was hydrogenated at atmospheric pressure over 10% palladium oxide on charcoal (25g, 50% wet paste, added as two charges). After 18hr, hydrogen uptake ceased and the catalyst was removed by filtration. The filtrate was evaporated in vacuo to approximately 50mL and concentrated hydrochloric acid (10mL) added. Evaporation was continued and most of the water removed by azeotropic distillation with IMS (3x100mL). The resulting suspension (~100mL) was aged at 5° for 1.5hr, filtered, and the residue washed with diisopropylether (2x100mL). The pale yellow solid (18.5g, 66% of theory) was dried in vacuo at 55° for 20h. Recrystallisation of a portion (15g) from water gave off-white crystals (13.2g, 88% of theory).

NMR:- 2.1 δ (4H) m; 2.64 δ (3H) d, J = 4.9Hz; 2.79 δ (3H) s; 3.04 δ m; 3.11 δ broad m, (5H); 3.33 δ (2H) m; 3.47 δ (2H) m; 7.0 (2H) m; 7.13 (1H) broad s; 7.31 δ (1H) d, J = 8.2Hz; 7.60 δ (1H) broad s; 10.6 δ (1H) broad resonance; 10.9 δ (1H) broad s.

Example 14N-Methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide,
hydrochloride

25 A mixture of (E)-N-methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]-ethenesulphonamide (10kg) and 10% palladium oxide on charcoal (10kg, 50% wet paste, added as two charges) in DMF (50L), water (35L) and 2N hydrochloric acid (15.75L) was hydrogenated at atmospheric pressure over 20.5h. The catalyst was removed by filtration. The filter cake was washed with water (40L). The filtrate was concentrated in vacuo to approximately 30L and cooled to 18°. Ethyl acetate (70L) was added over 1h and the resulting suspension cooled to 5° and aged for 1h. The product was collected by filtration, washed with ethyl acetate (20L) and dried in vacuo at 40-50° overnight (8.87kg, 79.0% of theory). A portion (0.2kg) of the solid was recrystallised from hot IMS/water (4:1) (1L) and obtained as fine, off-white crystals (0.143kg), 71.7% of theory).



NMR:- 2.1 δ (4H) m; 2.64 δ (3H) d, J = 4.9Hz; 2.78 δ (3H) s; 3.04 δ m, 3.11 δ broad m, (5H); 3.33 δ (2H) m; 3.47 δ (2H) m; 7.0 (2H) m; 7.13 (1H) broad s; 7.31 δ (1H) d, J = 8.2Hz; 7.58 δ (1H) broad s; 10.5 (1H) broad resonance; 10.9 (1H) broad s.

5

Example 15

N-Methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulphonamide, hydrochloride

10 A mixture of (E)-N-methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethanesulphonamide (8.6kg) and 10% palladium oxide on charcoal (2.58kg, 50% wet paste) in DMF (86L) and 2N hydrochloric acid (12.3kg) was hydrogenated at atmospheric pressure over 21h. The catalyst was removed by filtration. The filter cake was washed with DMF/water (1:1; 30L). The combined washings and filtrate were then treated with decolourising charcoal (0.86kg) at 15 75-80° for 2h. The suspension was filtered and the residue washed with DMF/water (2 x 30L). The filtrates from two hydrogenations could be combined for work-up. Thus the combined solutions were treated with 2M hydrochloric acid (1.72L) then concentrated *in vacuo* to approximately 52L. Ethyl acetate (120L) was added, the resulting suspension cooled to 3° and aged for 1h. The 20 product was collected by filtration, washed with ethyl acetate (2 x 26L) and dried *in vacuo* at 40-50° overnight (15.96kg, 83% of theory). Recrystallisation from hot IMS/water (7:1; 206L) gave fine, off-white crystals (13.02kg, 84% of theory).

25 NMR:- 2.1 δ (4H) m; 2.64 δ (3H) d, J = 4.9Hz; 2.78 δ (3H) s; 3.04 δ m, 3.11 δ broad m, (5H); 3.33 δ (2H) m; 3.47 δ (2H) m; 7.02 (2H) m; 7.12 (1H) broad s; 7.31 δ (1H) d, J = 8.2Hz; 7.62 δ (1H) broad s; 10.9 δ (2H) broad resonance.

Example 16

N-Methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulphonamide, hydrochloride

30 A mixture of (E)-N-methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethanesulphonamide (100g) and 10% palladium oxide on charcoal (30g, 50% wet paste) in DMF (1L) and 2N hydrochloric acid (150mL) was hydrogenated at atmospheric pressure over 48h. The catalyst was removed by filtration. The filter cake was washed with DMF/water (1:1; 200mL). The 35 combined washings and filtrate were then treated with decolourising charcoal

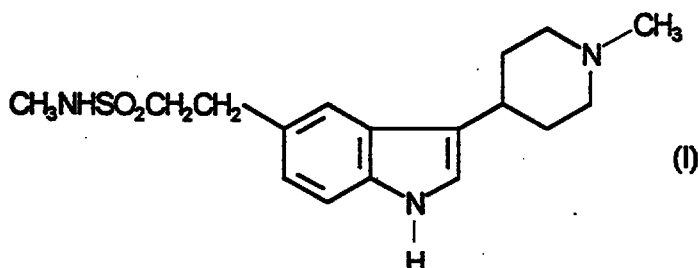


(10g) at 75-80° for 2h. The suspension was filtered, the residue washed with DMF/water (1:1; 400mL) and 2M hydrochloric acid (10mL) added. The filtrate was concentrated *in vacuo* to approximately 300mL and cooled to 30°. Ethyl acetate (700mL) was added over 30min and the resulting suspension cooled to 0-5° and aged for 30min. The product was collected by vacuum filtration and washed with ethyl acetate (150mL) followed by IMS (2 x 150mL). The IMS-damp cake was recrystallised from hot IMS/water (7:1) (1.315L) and obtained as fine, off-white crystals (60.1g, 54% of theory).

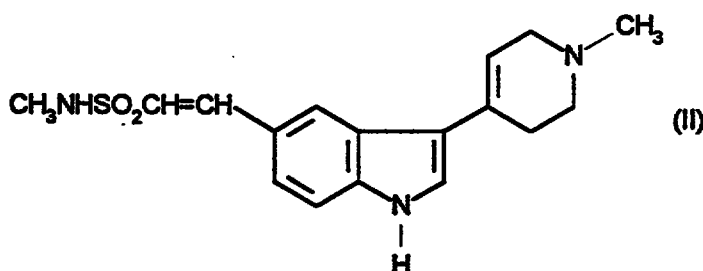
NMR:- 2.1 δ (4H) m; 2.62 δ (3H) d, J = 4.9Hz; 2.78 δ (3H) s; 3.02 δ m, 3.10 δ broad m, (5H); 3.31 δ (2H) m; 3.47 δ (2H) m; 6.98 (2H) m; 7.11 (1H) broad s; 7.29 δ (1H) d, J = 8.2Hz; 7.58 δ (1H) broad s; 10.5 (1H) broad resonance; 10.9 (1H) broad s.

**Claims**

1. A process for the preparation of the compound of formula (I)



5 or a salt thereof which comprises reducing the compound of formula (II)



or a salt thereof.

2. A process as claimed in claim 1 wherein the reduction process is carried out in the presence of hydrogen and a noble metal catalyst.

10 3. A process as claimed in claim 2 wherein the noble metal catalyst is palladium, palladium oxide, Raney nickel, platinum, platinum oxide or rhodium, optionally supported on charcoal.

4. A process as claimed in claim 3 wherein the noble metal catalyst is palladium oxide on charcoal.

15 5. A process as claimed in claim 4 wherein the noble metal catalyst is 10% palladium oxide on charcoal.

6. A process as claimed in claim 5 wherein the palladium oxide is added to the reaction vessel in the form of a wet paste.

20 7. A process as claimed in claim 1 wherein the reduction process is carried out in the presence of hydrogen and a homogenous catalyst.

8. A process as claimed in claim 7 wherein the homogenous catalyst is tris (triphenylphosphine) rhodium chloride.

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9. A process as claimed in any one of the preceding claims wherein the reduction process is carried out in a solvent comprising water or an alcohol, ether, ester or amide or a mixture thereof.

10. A process as claimed in claim 9 wherein the solvent is water, methanol, ethanol, dioxan, ethyl acetate, dimethylformamide or a mixture thereof.

11. A process as claimed in any one of the preceding claims wherein the reduction is carried out at a temperature of 10 to 50°C.

12. A process as claimed in claim 1 wherein the reduction process is carried out under conditions for catalytic hydrogen transfer.

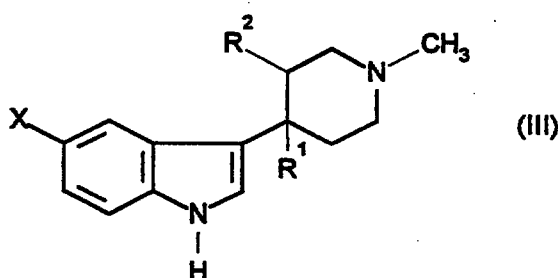
13. A process as claimed in claim 12 wherein the reduction process is carried out using palladium in the presence of a hydrogen donor.

14. A process as claimed in claim 13 wherein the hydrogen donor is formic acid or a salt thereof.

15. N-methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethenesulphonamide and salts thereof.

16. A process for the preparation of N-methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethenesulphonamide and salts thereof which comprises :

(A) condensing a compound of formula (III)



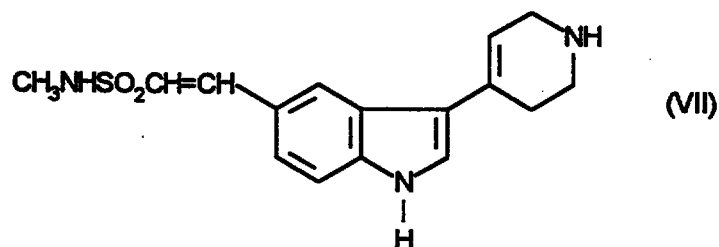
or a salt thereof, wherein R¹ is a hydroxy group and R² is hydrogen or R¹ and R² together form a double bond, X represents a leaving atom such as a halogen atom, for example a bromine atom, or a leaving group, for example a triflate (CF₃SO₃) group, with an N-methyl vinylsulphonamide of formula (IV)



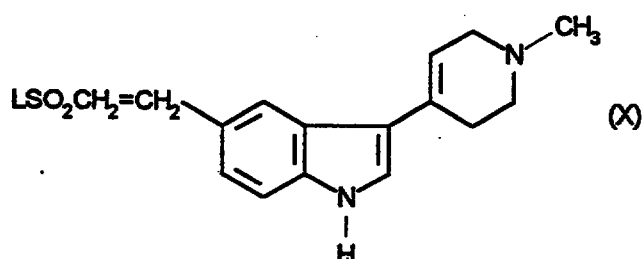
where Z is hydrogen or an amino protecting group, and optionally, if necessary and/or desired, deprotecting a protected derivative so obtained;



(B) methylating the compound of formula (VII)

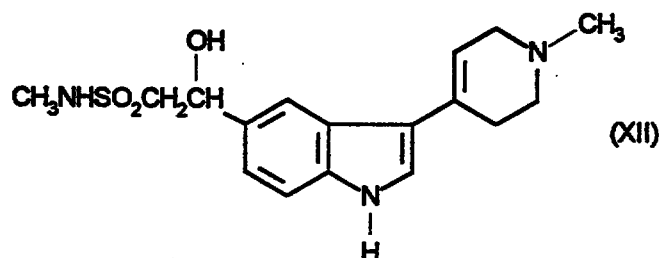


(C) condensing a compound of formula (X)



5 wherein L is a suitable leaving group, with methylamine;

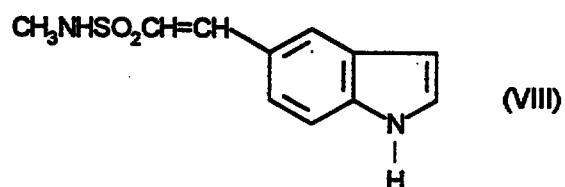
(D) dehydrating the compound of formula (XII)



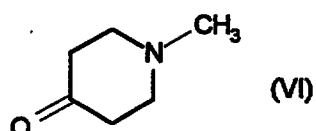
in the presence of an acid or a base;

(E) reacting the compound of formula (VIII)

10



with the compound of formula (VI)



; or



(F) dehydrating the compound of formula (XVI)

