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Oxford

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[54] **INDOLE DERIVATIVE**

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Related U.S. Application Data

[63] Continuation of Ser. No. 82,666, Aug. 7, 1987, abandoned, which is a continuation of Ser. No. 761,392, Aug. 1, 1985, abandoned.

[30] **Foreign Application Priority Data**

Aug. 1, 1984 [GB] United Kingdom 8419575

[51] **Int. Cl.**[5] **A61K 31/40;** C07D 209/16

[52] **U.S. Cl.** **514/415;** 548/504

[58] **Field of Search** 548/504; 514/415

[56] **References Cited**

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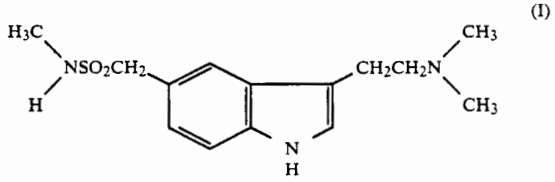
[57] **ABSTRACT**

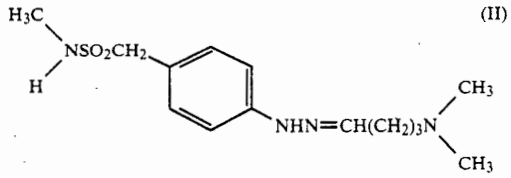
A compound of formula (I)



(I)

and its physiologically acceptable salts and solvates are described as useful in treating and/or preventing pain resulting from dilatation of the cranial vasculature in particular migraine.

The compound (I) may be prepared, for example, by cyclizing a compound of formula (II)



(II)

12 Claims, No Drawings

INDOLE DERIVATIVE

This application is a continuation, of application Ser. No. 082,666, filed Aug. 7, 1987 now abandoned, which is a continuation of Ser. No. 761,392, filed Aug. 1, 1985, which is now abandoned.

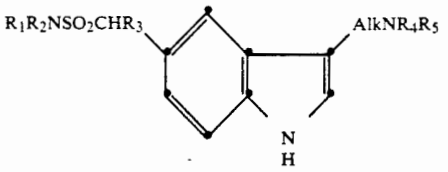
This invention relates to an indole derivative of use in the treatment of migraine, to processes for its preparation, to pharmaceutical compositions containing it and to its medical use.

The pain of migraine is associated with excessive dilatation of the cranial vasculature and known treatments for migraine include the administration of compounds having vasoconstrictor properties such as ergotamine. However, ergotamine is a non-selective vasoconstrictor which constricts blood vessels throughout the body and has undesirable and potentially dangerous side effects. Migraine may also be treated by administering an analgesic, usually in combination with an antiemetic, but such treatments are of limited value.

There is thus a need for a safe and effective drug for the treatment of migraine, which can be used either prophylactically or to alleviate an established headache, and a compound having a selective vasoconstrictor activity would fulfil such a role.

Furthermore, in conditions such as migraine, where the drug will usually be administered by the patient, it is highly desirable that the drug can be taken orally. It should therefore possess good bioavailability and be effectively absorbed from the gastro-intestinal tract so that prompt relief of symptoms can occur. The drug should also be safe (i.e. free from toxic effects) when administered by the oral route.

A wide variety of indole derivatives have been described as being of use in the treatment of migraine. In our published UK Patent Application No. 2124210A we describe indoles of the general formula

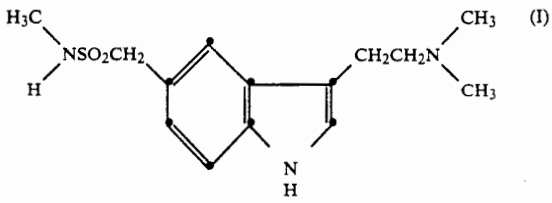


wherein R_1 represents a hydrogen atom or a C_{1-6} alkyl or C_{3-6} alkenyl group; R_2 represents a hydrogen atom or a C_{1-3} alkyl, C_{3-6} alkenyl, aryl, ar(C_{1-4})alkyl or C_{5-7} cycloalkyl group; R_3 represents a hydrogen atom or a C_{1-3} alkyl group; R_4 and R_5, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl or propenyl group or R_4 and R_5 together form an aralkylidene group; and Alk represents an alkylene chain containing two or three carbon atoms which may be unsubstituted or substituted by not more than two C_{1-3} alkyl groups, and physiologically acceptable salts and solvates thereof.

As indicated in UK Patent Application No. 2124210A, compounds of the above formula selectively constrict the carotid arterial bed of the anaesthetised dog and are thus potentially useful for the treatment of migraine.

We have now found a particular compound which falls within the scope of the group of compounds described and claimed in UK Patent Application No. 2124210A but which is not specifically disclosed therein, which compound has special advantages. Thus, we have discovered that by a selection of two specific substituents, namely the methylaminosulphonylmethyl group at the 5-position of the indole nucleus and the N,N-dimethylaminoethyl substituent at the 3-position, a compound having a combination of highly advantageous properties for the treatment of migraine is obtained.

Thus the present invention provides 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide, of formula (I)



(I)

and its physiologically acceptable salts and solvates (e.g. hydrates).

The compounds according to the invention are useful in treating and/or preventing pain resulting from dilatation of the cranial vasculature, in particular migraine and related disorders such as cluster headache.

The compound of formula (I) potently and selectively constricts the carotid arterial bed following intravenous administration as shown by tests in anaesthetised dogs. This potent and selective vasoconstrictor action has also been demonstrated in vitro. Further tests in anaesthetised dogs have shown that the compound of formula (I) is effectively and consistently well absorbed from the gastro-intestinal tract following intra-duodenal administration, quickly producing a sustained vasoconstriction in the carotid arterial bed.

At doses at which the compound of formula (I) would be efficacious in the treatment of migraine it has no significant effect on blood pressure and heart rate and no significant bronchoconstrictor effect on the lung.

The compound of formula (I) may safely be administered orally as well as intravenously.

The combination of these properties possessed by the compound of formula (I) is highly desirable in the treatment of migraine and the compound (I) has significant advantages, as demonstrated by the aforementioned experimental tests, over compounds which have previously been described as being of use in the treatment of migraine, such as those disclosed in published UK Patent Application No. 2124210A. It is particularly advantageous that the compound of formula (I) is effectively absorbed from the gastro-intestinal tract in a consistent manner.

Furthermore, tests in guinea pigs have shown that the compound of formula (I) promotes gastric emptying following oral administration, and hence relieves gastric stasis. Gastric stasis is a symptom commonly associated with migraine. Hence the ability of the compound of formula (I) to relieve gastric stasis is a further beneficial property of this compound in the treatment of migraine.

Suitable physiologically acceptable salts of the compound of formula (I) include acid addition salts formed with organic or inorganic acids for example hydrochlorides, hydrobromides, sulphates, nitrates, phosphates, formates, mesylates, citrates, benzoates, fumarates, ma-

leates and succinates. Other salts may be useful in the preparation of the compound of formula (I) e.g. creatinine sulphate adducts, and salts with e.g. toluene-p-sulphonic acid.

Where a salt of the compound (I) according to the invention is formed with a dicarboxylic acid, such as succinic acid, the salt may be formed with either one or both of the carboxylic acid groups, i.e. the salt may contain either one or two moles of the compound (I) per mole of acid. A preferred salt according to the invention is the succinate, most preferably the 1:1 succinate.

According to a further aspect, the invention provides a method of treatment of a human subject suffering from or susceptible to pain resulting from dilatation of the cranial vasculature, such as migraine or cluster headache, by administration of a compound of formula (I) or a physiologically acceptable salt or solvate thereof. The method of treatment preferably comprises oral administration of a compound of the invention.

Accordingly, the invention also provides a pharmaceutical composition adapted for use in medicine which comprises the compound of formula (I) and/or a physiologically acceptable salt or solvate (e.g. hydrate) thereof, formulated for administration by any convenient route. Such compositions may be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients. The compounds according to the invention may be formulated for oral, sub-lingual, parenteral, rectal or intra-nasal administration, or in a form suitable for administration by inhalation or insufflation. Formulations of the compounds for oral administration are preferred.

The pharmaceutical compositions for oral administration may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, sucrose, mannitol, maize starch, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. stearic acid, polyethylene glycol, magnesium stearate, talc or silica); disintegrants (e.g.) potato starch, sodium starch glycollate or croscarmellose sodium); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, aqueous or oily solutions, syrups, elixirs, emulsions or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives, glucose/sugar syrup, gelatin, aluminum stearate gel, or hydrogenated edible fats); emulsifying agents (e.g. lecithin, acacia or sorbitan mono-oleate); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid). The liquid preparations may also contain conventional buffers, flavouring, colouring and sweetening agents as appropriate.

A proposed dose of the compounds of the invention for oral administration to man (about 70 kg bodyweight) for the treatment of migraine is 0.1 mg to 100 mg, for example 0.5 mg to 50 mg, preferably 2 mg to 40 mg, of the active ingredient per dose which could be administered up to 8 times per day, more usually 1 to 4 times per day. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient, as well as the severity of the condition to be treated. It should be understood that unless otherwise indicated, the dosages are referred to in terms of the weight of compound (I) as the free base.

The compounds of the invention may be formulated for parenteral administration by injection, preferably intravenous or subcutaneous injection e.g. by bolus injection or continuous intravenous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents and/or agents to adjust the tonicity of the solution. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The overall daily dose administered by injection may be in the range 50 μg to 50 mg, e.g. 0.5 to 20 mg, which may for example be divided into 2,3 or 4 doses.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

Tablets for sub-lingual administration may be formulated in a similar manner to those for oral administration.

For intra-nasal administration the compounds of the invention may be used as a liquid spray or in the form of drops.

Dosages of the compounds of the invention for rectal, sublingual or intranasal administration to man (of average body weight e.g. about 70 kg) for the treatment of migraine may be similar to those described previously for oral administration.

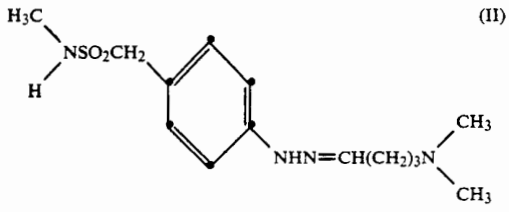
For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Aerosol formulations are preferably arranged so that each metered dose or "puff" delivered from a pressurized aerosol contains 0.2 mg to 2 mg of a compound of the invention, and each dose administered via capsules and cartridges in an insufflator or an inhaler contains 0.2 mg to 20 mg of a compound of the invention. Administration may be several times daily, for example from 2 to 8 times, giving for example 1, 2 or 3 doses each time. The overall daily dose by inhalation will be similar to that for oral administration.

The compounds of the invention may, if desired, be administered in combination with one or more other therapeutic agents, such as analgesics, anti-inflammatory agents and anti-nauseants.

The compound of formula (I) and its physiologically acceptable salts and solvates (e.g. hydrates) may be prepared by the general methods outlined hereinafter.

According to one general process (A), the compound of formula (I) may be prepared by cyclisation of the compound of formula (II)


(II)

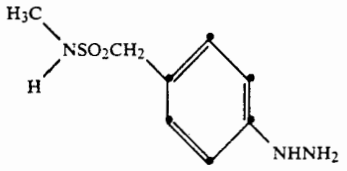
The reaction may conveniently be effected in aqueous or non-aqueous reaction media and at temperatures of from 10° to 200° C., preferably 50° to 125° C.

Particularly convenient embodiments of process (A) are described below.

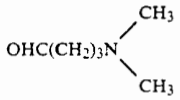
The cyclisation is desirably carried out in the presence of polyphosphate ester in a reaction medium which may comprise one or more organic solvents, preferably halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, dichlorodifluoromethane, or mixtures thereof. Polyphosphate ester is a mixture of esters which may be prepared from phosphorus pentoxide, diethylether and chloroform according to the method described in 'Reagents for Organic Synthesis', (Fieser and Fieser, John Wiley and Sons 1967).

Alternatively the cyclisation may be carried out in aqueous or non-aqueous media, in the presence of an acid catalyst. When an aqueous medium is employed this may be an aqueous organic solvent such as an aqueous alcohol (e.g. methanol, ethanol or isopropanol) or an aqueous ether (e.g. dioxan or tetrahydrofuran) as well as mixtures of such solvents and the acid catalyst may be for example an inorganic acid such as concentrated hydrochloric or sulphuric acid or an organic acid, such as acetic acid. (In some cases the acid catalyst may also act as the reaction solvent). In an anhydrous reaction medium, which may comprise one or more alcohols or ethers (e.g. as previously described) or esters (e.g. ethyl acetate), the acid catalyst will generally be a Lewis acid such as boron trifluoride, zinc chloride or magnesium chloride.

According to a particular embodiment of this cyclisation process, the compound of formula (I) may be prepared directly by the reaction of the compound of formula (III)


(III)

or a salt (e.g. the hydrochloride salt) thereof, with the compound of formula (IV)


(IV)

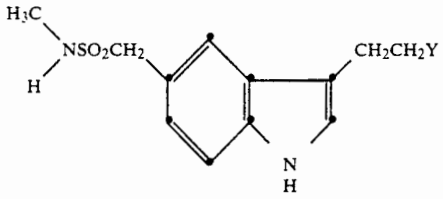
or a salt or protected derivative thereof (such as an acetal, for example, a dialkyl or cyclic acetal e.g. formed with an appropriate alkyl orthoformate or diol, or protected as a bisulphite addition complex), using the appropriate conditions as previously described for the cyclisation of the compound of formula (II). (The Fischer-Indole Synthesis, B. Robinson p488–Wiley 1982). It will be appreciated that in this embodiment of the cyclisation process (A) a compound of formula (II) is formed as an intermediate and reacted in situ to form the desired compound of formula (I).

The compound of formula (II) may, if desired, be isolated as an intermediate by reacting the compound of formula (III), or a salt or protected derivative thereof with the compound of formula (IV) or a salt or protected derivative thereof, in water or in a suitable solvent, such as an aqueous alcohol (e.g. methanol) or an aqueous ether (e.g. dioxan) and at a temperature of, for example, from 10° to 30° C. If an acetal of the compound of formula (IV) is used it may be necessary to carry out the reaction in the presence of an organic or inorganic acid (for example, acetic or hydrochloric acid).

The compound of formula (III) may be prepared for example as described in UK Patent Application No. 2124210A.

As illustrated in the following general processes (B) and (C), the dimethylamino substituent may be introduced at the 3-position by conventional techniques involving modification of a substituent at the 3-position or direct introduction of the aminoalkyl substituent into the 3-position.

Thus a further general process (B) for preparing the compound of formula (I) involves reacting a compound of general formula (V)


(V)

(wherein Y is a readily displaceable atom or group) or a protected derivative thereof, with dimethylamine.

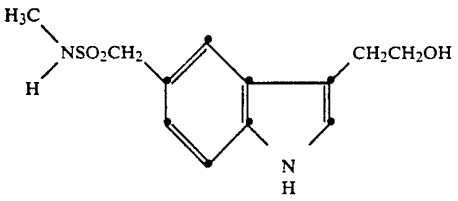
Suitable displaceable atoms or groups Y include a halogen atom (e.g. chlorine, bromine or iodine); a group OR_6 where OR_6 is, for example, an acyloxy group, which may be derived from a carboxylic or sulphonic acid, such as an acetoxy, chloroacetoxy, dichloroacetoxy, trifluoroacetoxy, p-nitrobenzoyloxy p-toluenesulphonyloxy or methanesulphonyloxy group; or a group $\oplus NR_7R_8R_9E\ominus$, where R_7, R_8 and R_9 each represents a C_{1-3} alkyl group, and E^- represents an anion such as a halide ion, e.g. a chloride, bromide or iodide ion.

The displacement reaction may conveniently be effected in an inert organic solvent (optionally in the presence of water), examples of which include alcohols, e.g. ethanol; cyclic ethers e.g. dioxan or tetrahydrofuran; acyclic ethers, e.g. diethylether; esters e.g. ethyl acetate; amides e.g. N,N-dimethylformamide; and ketones e.g. acetone, methylethylketone or methylisobutylketone. The process may be carried out at a temperature of, for example, −10° to +150° C., preferably 20° to 100° C.

The compounds of formula (V) wherein Y is a halogen atom may be prepared by reacting the hydrazine of formula (III) with an aldehyde (or a protected derivative thereof) of formula (VI)

$$OHC(CH_2)_3Y \quad (VI)$$

(wherein Y is as previously defined) in an aqueous alcohol (e.g. methanol) or an aqueous ether (e.g. dioxan) containing an acid (e.g. acetic or hydrochloric acid) or by reacting the compound of formula (VII)

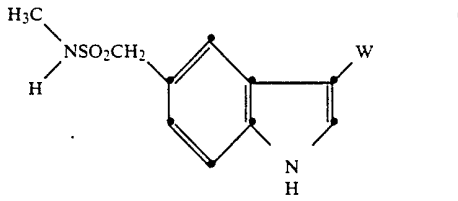


(VII)

with the appropriate halogenating agent such as a phosphorus trihalide, thionyl chloride or N-bromosuccinimide and triphenylphosphine, in a suitable solvent, for example pyridine or tetrahydrofuran. The compound of formula (VII) may also be used to prepare compounds of formula (V), wherein Y is a group OR_6 by acylation with the appropriate activated species derived from a carboxylic or sulphonic acid (e.g. an anhydride or sulphonyl chloride) using conventional techniques. The alcohol (VII) may be prepared for example by cyclisation of the appropriate hydrazone as described in UK Published Patent Application No. 2150932A.

Compounds of formula (V) where Y represents the group $\oplus NR_7R_8R_9E\ominus$ may be prepared from the corresponding primary amine by reaction with an appropriate alkylating agent, for example as described in general process (E) hereinafter.

The compound of formula (I) may also be prepared by another general process (C) involving reduction of a compound of general formula (VIII)



(VIII)

(wherein W is a group capable of being reduced to give the required dimethylaminoethyl group) or a salt or protected derivative thereof.

The required $—(CH_2)—_2$ and dimethylamino moieties may be formed by reduction steps which take place separately or together in any appropriate manner.

Groups which may be reduced to the $—(CH_2)—_2$ moiety include the corresponding unsaturated group and corresponding groups containing one or more carbonyl functions and/or a hydroxyl group.

The group W may be a group which is itself reduced to the dimethylaminoethyl moiety. Examples of such groups include $—(CH_2)_2N(CH_3)COR_{10}$ (where R_{10} represents a hydrogen atom, or an alkoxy or aralkoxy group); $—COCON(CH_3)_2$; $—CH_2CON(CH_3)_2$; $—CH(OH)CH_2N(CH_3)_2$; and $—COCH_2N(CH_3)_2$.

Alternatively W may represent a group which gives the dimethylaminoethyl moiety upon reduction in the presence of dimethylamine, for example $—CH_2CN$ and $—CH_2CHO$.

A particularly suitable method for preparing the compound of formula (I) is reductive methylation of the corresponding amino or methylamino derivative with formaldehyde in the presence of a suitable reducing agent. It will be appreciated that at least two equivalents of formaldehyde should be used when the starting material is the primary amine. If desired, the formaldehyde may first be condensed with the amine and the intermediate thus formed may subsequently be reduced.

Reduction of the compound of formula (VIII) may be effected by conventional methods, for example by catalytic hydrogenation or using a reducing agent such as an alkali metal or alkaline earth metal borohydride or cyanoborohydride. The reduction may conveniently be effected in an organic reaction medium which may comprise one or more organic solvents. Suitable solvents include alcohols, e.g. ethanol or propanol; cyclic ethers, e.g. dioxan or tetrahydrofuran; acyclic ethers e.g. diethyl ether; amides, e.g. dimethylformamide; esters, e.g. ethyl acetate, and nitriles e.g. acetonitrile.

It will be appreciated that the choice of reducing agent and reaction conditions will be dependent on the nature of the group W.

Suitable reducing agents which may be used in the above process for the reduction of compounds of formula (VIII) wherein W represents, for example, the group $—CH(OH)CH_2N(CH_3)_2$ include hydrogen in the presence of a metal catalyst, for example Raney Nickel or a noble metal catalyst such as platinum, platinum oxide, palladium or rhodium, which may be supported, for example, on charcoal, kieselguhr or alumina. In the case of Raney Nickel, hydrazine may also be used as the source of hydrogen. This process may conveniently be carried out in a solvent such as an alcohol e.g. ethanol, an ether, e.g. dioxan or tetrahydrofuran, an amide, e.g. dimethylformamide or an ester e.g. ethyl acetate, and at a temperature of from $-10°$ to $+50°$ C., preferably $-5°$ to $+30°$ C.

The reduction process may also be effected on compounds of formula (VIII) wherein W represents, for example, the group $—CH(OH)CH_2N(CH_3)_2$ or $—COCH_2N(CH_3)_2$ using an alkali metal or alkaline earth metal borohydride or cyanoborohydride e.g. sodium or calcium borohydride or cyanoborohydride which process may conveniently be carried out in an alcohol such as propanol, ethanol or methanol, and at a temperature of from 10° to 100° C., preferably 50° to 100° C. In some instances, the reduction using a borohydride may be carried out in the presence of cobaltous chloride.

Reductive methylation of the aminoethyl or methylaminoethyl compound corresponding to formula (I) with formaldehyde may be also effected using an alkali metal or alkaline earth metal borohydride or cyanoborohydride. The reaction may be effected in an aqueous or non-aqueous reaction medium, conveniently in an alcohol as just described, or an ether, e.g. dioxan or tetrahydrofuran, optionally in the presence of water. In this embodiment, the reaction may be effected in the presence of an acid e.g. acetic acid, and at a temperature in the range 0° to 100° C., preferably 5° to 50° C.

Reduction of compounds of formula (VIII) wherein W represents, for example, the groups $—(CH_2)_2N(CH_3)CHO$, $—CH_2CON(CH_3)_2$, $—CH(OH)CH_2N(CH_3)_2$, $—COCON(CH_3)_2$ and

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