

PATENT SPECIFICATION

NO DRAWINGS

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The inventors of this invention in the sense of being the devisers thereof within the meaning of Section 16 of the Patents Act 1949, are:—ERNST JUCKER STEINWEG, Ettingen/Baselland Switzerland and RUDOLF SÜSS, Stampfweg, Rheinfelden/Aargau, Switzerland, both Swiss citizens.

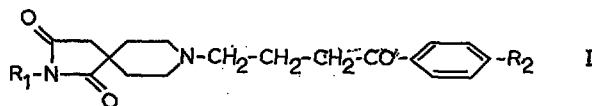
COMPLETE SPECIFICATION

Improvements in or relating to Substituted 2,8-Diazaspiro[4,5]decanes

We, SANDOZ PATENTS LIMITED, of 590 Jarvis Street, Toronto 5, Ontario, Canada, a Canadian Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new diazaspiro compounds and to a process for their production.

The present invention provides compounds of the general formula I,

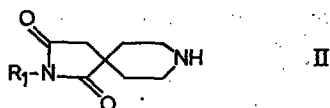


in which R₁ signifies a hydrogen atom, an alkyl radical containing from 1 to 4 carbon atoms inclusive or a benzyl radical, and

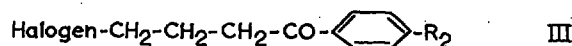
R₂ signifies a hydrogen atom, a fluorine, chlorine or bromine atom or an alkyl radical containing from 1 to 4 carbon atoms inclusive or an alkoxy radical containing from 1 to 4 carbon atoms inclusive,

their acid addition salts and pharmaceutical compositions containing, in addition to an inert carrier, a compound I and/or an acid addition salt thereof.

The present invention also provides a process for the production of the compounds I and their acid addition salts, characterised in that a substituted succinimide of general formula II,



in which R₁ has the above significance, is reacted with a compound of general formula III,



in which R₂ has the above significance,

[Price 4s. 6d.]

in the presence of an alkaline condensation agent, and, when an acid addition salt is desired, salification is effected with an organic or inorganic acid, e.g. hydrochloric, hydrobromic, sulphuric, citric, oxalic, tartaric, succinic, maleic, acetic, benzoic, hexahydrobenzoic, methanesulphonic, fumaric, gallic or hydriodic; it should be noted that an excess of compound II may be used as the alkaline condensation agent.

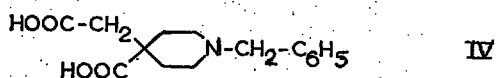
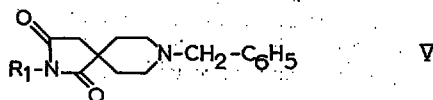
Compounds I at room temperature are colourless solid crystalline compounds which are easily soluble in the usual organic solvents, e.g. methanol, ethanol, acetone or benzene. With organic and inorganic acids they form salts which at room temperature are generally stable and crystalline.

Compounds I may be used as pharmaceuticals or in the production of pharmaceuticals. At least some of them have a peripheral and central action on the nervous system, e.g. sedation, narcosis potentiation and elevation of the convulsive threshold. They inhibit the conditioned escape reaction in rats as well as emotional stress reactions, and decrease spontaneous activity of mice and excitation caused by amphetamine administration in animals. Some of the compounds I may be used as neuroleptics in the treatment of a great variety of psychic excitation syndromes. 2 - Methyl - 8 - (4' - *p*-fluorophenyl - 4' - oxo - butyl) - 2,8 - diazaspiro[4,5]decane - 1,3 - dione is a particularly good neuroleptic, e.g. for treating agitated psychoses. Furthermore, 2 - ethyl - 2-isopropyl - and 2 - benzyl - 8 - (4' - *p* - fluorophenyl - 4' - oxobutyl) - 2,8 - diazaspiro[4,5]decane - 1,3 - dione are endowed with excellent neuroleptic properties. All the other exemplified compounds have useful pharmacodynamic properties of the kind mentioned herein and are therefore indicated for use as pharmaceuticals.

Some of the compounds III are known; those which are unknown may be produced in a manner analogous to the following method of producing 4-chloro-*p*-methylbutyrophenone. 800 cc of absolute toluene and 141 g of aluminium chloride (1.06 mol) are mixed in a flask and brought to a temperature of 15°C. by cooling with ice water. 141 g (1 mol) of γ -chlorobutyric acid chloride are then added dropwise whilst cooling with ice water, at such a rate that the temperature does not exceed 15–20°C.; this addition generally required approximately 20 minutes. The mixture is stirred for a further 20 minutes at this temperature and the reaction mixture then poured onto ice. 40 cc of concentrated hydrochloric acid are added, the mixture cooled and extracted a number of times with ether. The combined ether extracts are washed three times with a dilute soda solution, dried over calcium chloride and the ether evaporated. After distilling once in a high vacuum, the compound is sufficiently pure for the next reaction. For the purpose of analysis, distillation in a high vacuum is repeated; pure 4-chloro-*p*-methylbutyrophenone boils at 109°/0.07 mm of Hg. $n_D^{20} = 1.5414$.

Should absolute benzene or some other substituted anhydrous benzene, e.g. chloro, bromo or tertiary butyl benzene, anisol or phenetol, be used instead of absolute toluene in the above described reaction, the corresponding substituted 4-chloro-butyrophenones result; with the above mentioned substituents the conversion of the γ -chloro-butyric acid chloride with the phenyl radical occurs in the *p*-position.

The compounds II used as starting materials may, for example, be prepared as follows: 1-benzyl-4-piperidone is converted to the required (1-benzyl-4-piperidylidene)-cyanoacetic acid alkyl ester in an inert organic solvent, e.g. benzene, toluene, xylene or tetraline, with a suitable cyanoacetic acid alkyl ester in the presence of a catalyst for splitting off water or such a catalyst mixture, e.g. glacial acetic acid and ammonium acetate, and in the presence of a continuous water separator. The elements of hydrocyanic acid are added at the double bond of this derivative and the resulting compound is saponified with concentrated hydrochloric acid and decarboxylated to the corresponding substituted succinic acid of formula IV below. Compound IV is esterified with an absolute alkanol and hydrogen chloride to form the corresponding dialkyl ester. The substituted succinic acid diester is converted to the desired substituted 8-benzyl-2,8-diazaspiro[4,5]decane-1,3-dione of formula V by heating with a nitrogen compound of general formula R_1-NH_2 , in which R_1 has the above significance, e.g. concentrated aqueous ammonia or a primary alkylamine, e.g. methylamine, ethylamine, or benzylamine, preferably in a closed vessel. For the purpose of quantitative cyclisation the mixture is heated, e.g. to 180–250°C., at normal pressure. Compound V is then hydrogenated in a liquid aliphatic alcohol with hydrogen in the presence of a palladium catalyst until no further hydrogen is taken up. The resulting compound II may be purified by distillation in a vacuum or by recrystallisation of its salts.



R₁ has the above significance.

The compounds of the invention may be employed as pharmaceuticals as such, or in the form of appropriate medicinal preparations for administration, e.g. enterally, parenterally or intranasally. In order to produce such medicinal preparation, the compounds of the invention are worked up with inorganic or organic adjuvants which are physiologically inert. Examples of such adjuvants or carriers for various medicinal preparations are as follows:—

- (1) Tablets and dragees: lactose, starch, talc and stearic acid.
- (2) Syrups : solutions of cane sugar, invert sugar and glucose.
- (3) Injectable solutions : water, physiologically acceptable alcohols, glycerine and physiologically acceptable vegetable fats.
- (4) Suppositories : physiologically acceptable, natural or hardened oils and waxes.
- (5) Ointments, suspensions and emulsions : inorganic and organic, dipophilic or hydrophilic compounds, paraffin, alginates, cellulose derivatives, polyoxyethylene derivatives, bentonite and petroleum jelly.

The preparations may contain suitable preserving, stabilizing or wetting agents, solubilizers, sweetening and colouring substances or flavourings, with the proviso that they must be physiologically acceptable in so far as they are for internal use.

The present invention also provides pharmaceutical compositions containing, in addition to an inert, physiologically acceptable carrier, a compound of formula I above and/or an acid addition salt thereof.

In the following non-limitative Examples all temperatures are stated in degrees Centigrade. The melting and boiling points are corrected.

EXAMPLE 1: 2 - methyl - 8 - (4¹ - p - fluorophenyl - 4¹ - oxo - butyl) - 2,8 - diazaspiro[4,5]decane - 1,3 - dione.

4.1 g of 2 - methyl - 2,8 - diazaspiro[4,5]decane - 1,3 - dione, 4.8 g of 4 - chloro - p - fluoro - butyrophenone and 8 g of anhydrous soda in 50 cc of *n*-butanol are heated to 120° for 24 hours. The solution is then decanted from the soda. A portion of the condensation product already precipitates whilst still warm. The mixture is filtered whilst hot, evaporated to dryness and the residue extracted with ethanol. The ethanol extract is combined with the filter residue from above, an excess of 2 N hydrochloric acid poured over the substance, which is only slightly soluble in all the usual solvents, and the solution evaporated in a vacuum at 80° until dry. The remaining residue is recrystallised firstly from ethanol and then from water. 2 - Methyl - 8 - (4¹ - p - fluorophenyl - 4¹ - oxo - butyl) - 2,8 - diazaspiro[4,5]decane - 1,3 - dione hydrochloride melts at 285—286°.

The 2 - methyl - 2,8 - diazaspiro[4,5]decane - 1,3 - dione used as a starting material may, for example, be produced as follows: Cyanoacetic acid ethyl ester and 1-benzyl-4-piperidone are heated at reflux with some glacial acetic acid and ammonium acetate in benzene with continuous separation of water, (1 - benzyl - 4 - piperidylidene)-cyanoacetic acid ethyl ester resulting; from ether/petroleum ether yellow crystals having a melting point of 70—71°. By treating the piperidylidene compound with potassium cyanide in aqueous ethanol the elements of hydrocyanic acid are added at the double bond, the resulting compound is saponified with hydrochloric acid and decarboxylated and the resulting substituted succinic acid esterified with absolute ethanolic hydrogen chloride. [(1 - Benzyl - 4 - ethoxy - carbonyl - piperidyl) - 4] - acetic

acid ethyl ester boils at 150°/0.03 mm of Hg (temperature measured in the air bath); light yellow oil. The diester is heated to 180° with liquid methylamine in a closed vessel; after cooling, the excess of methylamine is left to evaporate and the crystalline residue heated to 200°, whereby methylamine and ethanol are split and the residue melts 2 - Methyl - 8 - benzyl - 2,8 - diazaspiro[4,5]decane - 1,3 - dione crystallises from ethanol in large colourless prisms having a melting point of 111—112°. The compound is hydrogenated in ethanol with hydrogen in the presence of a palladium catalyst on activated charcoal at normal pressure and room temperature. 2 - methyl - 2,8-diazaspiro[4,5]decane - 1,3 - dione boils at 99°/0.02 mm of Hg (temperature measured in an air bath); strongly hygroscopic substance which crystallises in rectangular prisms having a melting point of 67°.

EXAMPLE 2: 2 - methyl - 8 - (4¹ - *p* - fluorophenyl - 4¹ - oxo - butyl) - 2,8-diazaspiro[4,5]decane - 1,3 - dione.

23.1 g of 2-methyl-2,8-diazaspiro[4,5]decane-1,3-dione (0.127 mol), 12.7 g of 4 - chloro - *p* - fluoro - butyrophenone (0.0635 mol) and 0.1 g of potassium iodide are heated to 130° in 80 cc of absolute toluene for 36 hours in a closed vessel. After cooling the crystalline reaction mixture is washed out with benzene and filtered; the residue consists of 2 - methyl - 2,8 - diazaspiro[4,5]decane - 1,3 - dione hydrochloride, melting point 281° after drying in a water jet vacuum. The filtrate is freed of the solvent in a vacuum at 70°. A red oil results which crystallises upon acidification to Congo Red with ethanolic hydrochloric acid. 40 cc of ether are added and the solution filtered after standing for 4 hours in the ice box. The residue is recrystallised from water; 2-methyl-8 - (4¹ - *p* - fluorophenyl - 4¹ - oxo - butyl) - 2,8 - diazaspiro[4,5]decane - 1,3 - dione hydrochloride melts at 285—286°.

In Table I below there are shown examples in which the hydrochlorides of 2-methyl - 8 - (4¹ - *R*₂ - phenyl - 4¹ - oxo - butyl) - 2,8 - diazaspiro[4,5]decane - 1,3-diones are produced from 2 - methyl - 2,8 - diazaspiro[4,5]decane - 1,3 - dione and the corresponding *p*-substituted 4-halogeno-butyrophenones in manner analogous to that described in Example 1.

TABLE I

Example No.	R ₂	M.p. after crystallisation from
3	H	257° aqueous methanol with the addition of ether
4	Chlorine	285—287° water
5	Bromine	275—277° water
6	Methyl	270° methanol
7	Methoxy	265° aqueous ethanol with the addition of ether
8	Tert.-butyl	294° 95% aqueous ethanol

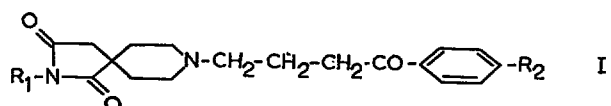
The 2 - *R*₁ - 8 - (4¹ - *p* - fluorophenyl - 4¹ - oxo - butyl) - 2,8 - diazaspiro[4,5]decane - 1,3 - diones shown in Table II below are produced from 4 - chloro - *p* - fluoro butyrophenone and the corresponding 2-substituted 2,8 - diazaspiro[4,5]decane-1,3-diones in a manner analogous to that described in Example 1. The properties of the starting materials II and the compounds V are also shown in Table II. The production of compounds II is effected in a manner analogous to that described in Example 1.

TABLE II

Example No.	Compound	M.p. or b.p.	M.p. determined after crystallisation from
9 $R_1 = \text{ethyl}$	I (hydrochloride)	282—284° (decomp.)	Methanol
	II (free base)	118°/0.06 mm of Hg colourless oil	—
	V (free base)	104°	Ethanol
10 $R_1 = \text{iso-propyl}$	I (hydrochloride)	276—278°	Ethanol
	II (free base)	110°/0.05 mm of Hg colourless oil, crystallising upon cooling, m.p. 79—82°	—
	V (hydrochloride)	298—302° (decomp.)	Ethanol
11 $R_1 = n\text{-butyl}$	I (free base)	95°	Ethanol
	Neutral naphthalene-1,5-disulphonate	239—241°	Methanol
	II	120/0.06 mm of Hg colourless oil, crystallising upon cooling, m.p. 60°	—
	V (hydrochloride)	273°	Ethanol
12 $R_1 = \text{benzyl}$	I (free base)	120—122°	Methanol
	II (free base)	196/0.1 mm of Hg colourless, viscous oil	—
	V (hydrochloride)	236—238°	Methanol with the addition of ether

WHAT WE CLAIM IS:—

1. A process for the production of compounds of the general formula I,



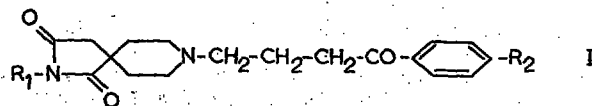
- 5 in which R_1 signifies a hydrogen atom, an alkyl radical containing from 1 to 4 carbon atoms inclusive or a benzyl radical, and
- 5 R_2 signifies a hydrogen atom, a fluorine, chlorine or bromine atom or an alkyl radical containing from 1 to 4 carbon atoms inclusive or an alkoxy radical containing from 1 to 4 carbon atoms inclusive,
- 10 and their acid addition salts, characterised in that a substituted succinimide of general formula II,
- 10

TABLE II

Example No.	Compound	M.p. or b.p.	M.p. determined after crystallisation from
9 $R_1 = \text{ethyl}$	I (hydrochloride)	282—284° (decomp.)	Methanol
	II (free base)	118°/0.06 mm of Hg colourless oil	—
	V (free base)	104°	Ethanol
10 $R_1 = \text{iso-propyl}$	I (hydrochloride)	276—278°	Ethanol
	II (free base)	110°/0.05 mm of Hg colourless oil, crystallising upon cooling, m.p. 79—82°	—
	V (hydrochloride)	298—302° (decomp.)	Ethanol
11 $R_1 = n\text{-butyl}$	I (free base)	95°	Ethanol
	Neutral naphthalene-1,5-disulphonate	239—241°	Methanol
	II	120/0.06 mm of Hg colourless oil, crystallising upon cooling, m.p. 60°	—
	V (hydrochloride)	273°	Ethanol
12 $R_1 = \text{benzyl}$	I (free base)	120—122°	Methanol
	II (free base)	196/0.1 mm of Hg colourless, viscous oil	—
	V (hydrochloride)	236—238°	Methanol with the addition of ether

WHAT WE CLAIM IS:—

1. A process for the production of compounds of the general formula I,

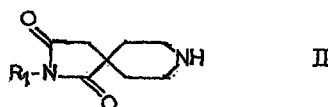


5 in which R_1 signifies a hydrogen atom, an alkyl radical containing from 1 to 4 carbon atoms inclusive or a benzyl radical, and

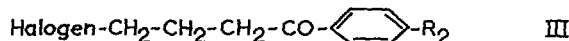
R_2 signifies a hydrogen atom, a fluorine, chlorine or bromine atom or an alkyl radical containing from 1 to 4 carbon atoms inclusive, or an alkoxy radical containing from 1 to 4 carbon atoms inclusive,

10 and their acid addition salts, characterised in that a substituted succinimide of general formula II,





in which R_1 has the above significance,
is reacted with a compound of general formula III,



- 5 in which R_2 has the above significance, 5
in the presence of an alkaline condensation agent, and, when an acid addition salt is
desired, salification is effected with an organic or inorganic acid.
2. A process for the production of compounds of the general formula I stated
in claim 1, substantially as herein described with reference to any one of the examples.
- 10 3. The compounds of the general formula I stated in claim 1, whenever pro- 10
duced by the process claimed in either one of the preceding claims, and their acid
addition salts.
4. The compounds having the general formula I stated in claim 1 and their acid
addition salts.
- 15 5. 2 - Methyl - 8 - (4¹ - *p* - fluorophenyl - 4¹ - oxo - butyl) - 2,8 - diazaspиро- 15
[4,5]decane - 1,3 - dione.
6. 2 - Methyl - 8 - (4¹ - phenyl - 4¹ - oxo - butyl) - 2,8 - diazaspиро[4,5]-
decane - 1,3 - dione.
- 20 7. 2 - Methyl - 8 - (4¹ - chlorophenyl - 4¹ - oxo - butyl) - 2,8 - diazaspиро- 20
[4,5]decane - 1,3 - dione.
8. 2 - Methyl - 8 - (4¹ - bromophenyl - 4¹ - oxo - butyl - 2,8 - diazaspиро[4,5]-
decane - 1,3 - dione.
- 25 9. 2 - Methyl - 8 - (4¹ - methylphenyl - 4¹ - oxo - butyl - 2,8 - diazaspиро- 25
[4,5]decane - 1,3 - dione.
10. 2 - Methyl - 8 - (4¹ - methoxyphenyl - 4¹ - oxo - butyl - 2,8 - diazaspиро- 25
[4,5]decane - 1,3 - dione.
11. 2 - Methyl - 8 - (4¹ - *t* - butylphenyl - 4¹ - oxo - butyl - 2,8 - diazaspиро-
[4,5]decane - 1,3 - dione.
- 30 12. 2 - Ethyl - 8 - (4¹ - *p* - fluorophenyl - 4¹ - oxo - butyl - 2,8 - diazaspиро- 30
[4,5]decane - 1,3 - dione.
13. 2 - Isopropyl - 8 - (4¹ - *p* - fluorophenyl - 4¹ - oxo - butyl - 2,8 - diazaspиро-
[4,5]decane - 1,3 - dione.
- 35 14. 2 - *n* - butyl - 8 - (4¹ - *p* - fluorophenyl - 4¹ - oxo - butyl - 2,8 - diazaspиро- 35
[4,5]decane - 1,3 - dione.
15. 2 - Benzyl - 8 - (4¹ - *p* - fluorophenyl - 4¹ - oxo - butyl - 2,8 - diazaspиро- 35
[4,5]decane - 1,3 - dione.
16. The acid addition salts of the compounds claimed in any one of claims 5 to
15.
- 40 17. Pharmaceutical compositions containing, in addition to an inert physiologi- 40
cally acceptable carrier, a compound claimed in any one of claims 3 to 16.

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