

PATENT SPECIFICATION

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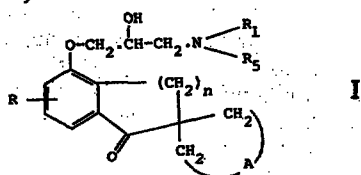


(54) IMPROVEMENTS IN OR RELATING TO SPIROCYCLIC COMPOUNDS

(71) We, SANDOZ LTD., of 35 Lichstrasse, 4002 Basle, Switzerland, a Swiss 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 3 - amino-2 - hydroxypropoxyphenyl derivatives.

The present invention provides a compound of formula I,



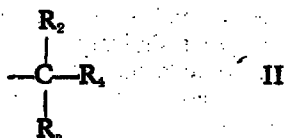
wherein

A is a straight chain alkylene of 2 to 4 carbon atoms, or straight chain alkenylene of 2 to 4 carbon atoms,

n is 1, 2 or 3,

R is hydrogen or halogen of atomic number from 9 to 35, and

either (i) R₁ is a group of formula II,



wherein

R₂ and R₃, independently, are hydrogen or alkyl of 1 to 4 carbon atoms, and

R₄ is alkyl of 1 to 4 carbon atoms, alkoxy-alkyl of 2 to 5 carbon atoms, alkylthio-alkyl of 2 to 5 carbon atoms, phenylalkyl or phenoxyalkyl or phenylthioalkyl,

wherein the alkyl moiety has from 1 to 3 carbon atoms, or phenyl, the phenyl ring of each of the last four radicals being unsubstituted or mono-substituted by, or disubstituted independently by, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, hydroxy or halogen of atomic number from 9 to 35, and

R₅ is hydrogen,

or (ii) R₁ and R₅ together with the nitrogen atom to which they are bound are

- (a) 2,2,6,6-tetramethylpiperidinyl,
 (b) 2,2,5,5-tetramethylpyrrolidinyl, or
 (c) piperazinyl substituted in the 4-position by alkyl of 1 to 4 carbon atoms or phenyl which is unsubstituted, or mono-substituted by, or di- or tri-substituted independently by, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halogen of atomic number from 9 to 35.

In a compound of formula I any alkyl or alkylene moiety, e.g. in alkoxyalkyl, except where otherwise stated, has preferably 2 carbon atoms or especially one carbon atom.

Halogen is preferably chlorine.

Preferably A is alkylene of 2 or 3 carbon atoms, or alkenylene of 2 carbon atoms. When A is alkenylene the double bond has the cis configuration.

When A is alkenylene of 4 carbon atoms it is preferably 2-butenylene.

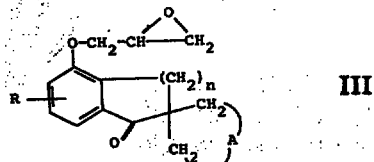
n is preferably 1.

R is preferably hydrogen. When it is halogen, it is preferably in the ring position meta or para to the oxygen atom attached to the phenyl ring.

R₁ is preferably a group of formula II. At least one of R₂ and R₃ is preferably alkyl.

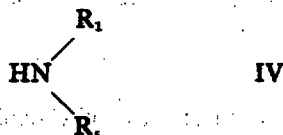
R_1 is preferably alkyl. Any phenyl ring contained in R_1 is preferably unsubstituted. A preferred phenyl ring substituent with regard to R_1 is hydroxy. R_1 is especially tert.-butyl.

- 5 The present invention also provides a process for the production of a compound of formula I which comprises reacting a compound of formula III,



- 10 wherein

A, n and R are as defined above, or a reactive functional derivative thereof, with a compound of formula IV,

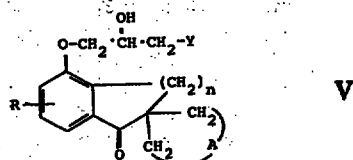


- 15 wherein

R_1 and R_2 are as described above.

- 20 The reaction may be effected in conventional manner for the reaction of an epoxide or a reactive functional derivative thereof with an amine to form a β -hydroxyalkylamine.

Suitable reactive functional derivatives of the compound of formula III include compounds of formula V,



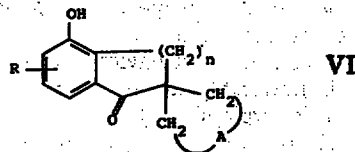
- 25 wherein

A, n, R are as defined above, and Y is a leaving group, e.g. chlorine, bromine, iodine, mesyloxy or tosyloxy.

- 30 The reaction may be effected in an inert solvent such as dioxane. Alternatively when the amine of formula IV is liquid, this may be used as the reaction medium.

Suitable temperatures are from about 20° to about 150°C.

- 35 A compound of formula III may be obtained by reacting a compound of formula VI,

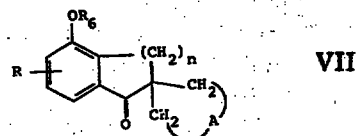


wherein

- 40 A, n and R are as defined above, with epichlorohydrin in the presence of piperidine.

A compound of formula VI may be ob-

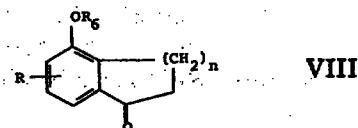
tained by demethylating or debenzylating a compound of formula VII,



wherein

A, n and R are as defined above, and R_6 is methyl or benzyl.

A compound of formula VII may be obtained by alkylating a compound of formula VIII,



wherein

n, R and R_6 are as defined above, with a compound of formula IX,



wherein

A is as defined above.

Insofar as the production of any particular starting material is not particularly described, this may be produced and purified according to known processes, or analogous to known processes. Thus a compound of formula V may be obtained by reacting a compound of formula III with a compound HY, wherein Y is as defined above.

Free base forms of the compounds of formula I may be converted into acid addition salt forms in conventional manner and vice versa. Suitable acids for salt formation include hydrochloric acid, maleic acid, malonic acid, fumaric acid and tartaric acid.

Compounds of formula I may exist in racemic or individual optical isomer form. Individual optical isomer forms may be obtained in conventional manner from the racemic form, by fractional crystallization of the tartrate diastereomeric salts. Alternatively, the individual optical isomers may be made using optically active starting materials, e.g. the compound of formula III, in a conventional stereospecific synthesis for analogous optically active 3-amino-2-hydroxypropoxyaryl derivatives.

In the following Examples all temperatures are in degrees Centigrade and are uncorrected.

EXAMPLE 1.

4' - (3-tert.-butylamino-2-hydroxypropoxy) - spiro(cyclohexane - 1,2'-indan) - 1' - one.

1) *Racemic form.*

7.5 g of a mixture of mainly 4' - (3-chloro-2-hydroxypropoxy) - spiro(cyclohexane - 1,2' - indan) - 1' - one and of 4' -

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- (2,3 - epoxypropoxy) - spiro(cyclohexane-1,2' - indan) - 1' - one in 50 ml dioxane and 30 ml tert.-butylamine are heated at 130° for 20 hours in an autoclave, then cooled and partitioned between 2N tartaric acid and ether. The aqueous phase is made alkaline and extracted with ether. The organic phases are evaporated to yield the title compound in free base form (M.Pt. 87°—88°) which is converted into the hydrogen maleate; M.Pt. 180°—181°, and hydrogen malonate M.Pt. 143°—145°.
- The starting material is obtained as follows:—
- 15 a) A solution of 20 g 4 - methoxyindan-1 - one and 24 g 1,5-dibromopentane in 150 ml benzene is added quickly dropwise to a solution of potassium tert.-butylate (produced from 9.7 g potassium and excess tert.-butanol) in 200 ml benzene at 80°. The mixture is refluxed for 4 hours, treated with 50 ml water and 200 ml 2N hydrochloric acid, and extracted with benzene. Chromatography on silicagel of the benzene phase gives 4' - methoxy-spiro(cyclohexane - 1,2' - indan) - 1' - one. M.Pt. 94°—96°.
 - 20 b) 5.6 g of 4' - methoxy - spiro(cyclohexane - 1,2' - indan) - 1' - one in 80 ml acetic acid and 20 ml 48% (w/w) aqueous hydrogen bromide are refluxed for 20 hours. The mixture is evaporated, diluted with water and extracted with ether. Evaporation of the solvent yields 4' - hydroxy - spiro(cyclohexane-1,2' - indan) - 1' - one; M.Pt. 162°—164° (from ethanol).
 - 25 c) To 4.5 g of 4' - hydroxy - spiro(cyclohexane 1 1,2' - indan) - 1' - one and 20 ml epichlorohydrin are added 2 drops of piperidine. The mixture is stirred at 100°C for 4 hours. Evaporation and taking up of the residue in ether yields the starting material mixture as an oil on evaporation.
 - 30 2) *Optically active forms.*
38 g of 4' - (3 - tert. - butylamino - 2-hydroxypropoxy) - spiro(cyclohexane - 1,2-indan - 1' - one in free base form in 300 ml methanol is treated with a solution of 16.5 g (L+) - tartaric acid in 150 methanol. The resultant crystalline precipitate is filtered off and crystallized several times from methanol to yield 4' - [(2S) - 3 - tert.-butylamino - 2 - hydroxypropoxy - spiro(cyclohexane - 1,2' - indan) - 1' - one (L+) -tartrate. M.Pt. 224°—226°. This tartrate is converted into the free base by treatment with a mixture of aqueous sodium hydroxide and ether. The free base is converted by treatment with one equivalent of malonic acid in ethanol/ether into the hydrogen malonate of the 2(S) isomer of the title compound. This compound crystallises in a solvated form (M.Pt. 64°—66°) which on drying at 60°/0.002 mm is converted to the solvent-free, higher melting product, M.Pt. 124°—126° [α]_D²⁰ = -11.4° (± 0.8°) (c = 2.0 in CHCl₃).
 - 35 The filtrate obtained on filtering off the crystalline precipitate of the L(+) tartrate salt is treated with aqueous sodium hydroxide/ether yielding a free base mixture. 32 g of this free base mixture is treated with 16.5 g (D-) tararic acid as described in the preceding paragraph to afford 4' - [(2R) - 3-tert. - butylamino - 2 - hydroxypropoxy)-spiro(cyclohexane - 1,2' - indan) - 1' - one (D-) - tartrate; M.Pt. 224°—226°, and the corresponding (2R) hydrogen malonate; M.Pt. 124°—126° [α]_D²⁰ = +11.6° (± 0.8°) (c = 2.0 in CHCl₃).
 - 40 In analogous manner to Example 1, the following compounds of formula I in racemic and optically active form may be produced, wherein R = H, and

Ex. No.	R _s	R _i	n	A	M.Pt. of racemic form
1A	H	-C(CH ₃) ₃	2	-(CH ₂) ₃	220°—222°)
1B	H	-C(CH ₃) ₃	1	-(CH ₂) ₂	220°—222°)
1C	H	-C(CH ₃) ₃	2	-(CH ₂) ₄	215°—217°)
1D	H	-C(CH ₃) ₃	2	-(CH ₂) ₇	201°—203°)
1E	H	-C(CH ₃) ₃	1	-(CH ₂) ₇	165°—170°)
1F	-C(CH ₃) ₂ -(CH ₂) ₂ -C(CH ₃) ₂ -		1	-(CH ₂) ₂	233°—235°)

-) hydrogen maleate
) fumarate
) hydrochloride

The compounds of formula I exhibit pharmacological activity in animals. In particular, the compounds of formula I inhibit glycerol release stimulated by isoproterenol in standard tests, e.g. *in vitro* with fat cells of the epididymal fat pads isolated in accordance with the method of M. Rodbell [J. Biol. Chem. 239 (1964), 375-380], in the presence of 10^{-8} to 10^{-7} Molar solution of the compounds.

Alternatively the inhibition of glycerol release may be observed *in vivo* using rats in conventional manner on administration s.c. of from about 0.03 to about 10 mg/kg animal body weight of the compounds.

The compounds are therefore indicated for use in the treatment of the increase of free fatty acid concentration in the blood induced by emotional stress, and also inhibit lipolysis induced by emotional stress, and myocardial infarction induced by emotional stress.

Additionally, the compounds inhibit hyperglycemia induced by emotional stress as indicated by an inhibition of glycogenolysis induced by isoproterenol in standard tests, e.g. *in vivo* in rats in conventional manner on administration s.c. of from about 0.03 to about 10 mg/kg animal body weight of the compounds.

The compounds are therefore indicated for use in the treatment of hyperglycemia induced by emotional stress, e.g. for suppressing of appetite induced by emotional stress.

For these stress indications an indicated daily dose is from about 10 to about 500 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 2 to about 250 mg of the compound or in sustained release form.

Additionally, the compounds exhibit a cardio-vascular adrenergic β -blocking effect as indicated in standard tests. For example, the compounds, at a concentration of from 0.08×10^{-8} to 10×10^{-8} Molar in the spontaneously beating isolated guinea pig atrium, inhibit the positive inotropic and positive chronotropic adrenaline effect. Additionally, the compounds on administration i.v. of from 0.02 mg/kg to 1 mg/kg to the anaesthetized cat inhibit the isoproterenol-induced tachycardia and blood pressure lowering in the infusion cat test.

The compounds are therefore indicated for use as cardio-vascular adrenergic β -blocking agents, e.g. for the prophylaxis and therapy of Angina pectoris, and also as arrhythmics.

In general, the 2(S) optical isomers are more active than the 2(R) optical isomers.

As indicated daily dose is from about 10 to about 500 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 2 to about

250 mg of the compounds or in sustained release form.

The compounds of formula I also exhibit a salidiuretic effect as indicated in standard tests, e.g. in the diuretic rat test in accordance with the principles of E. Flückiger et al, Schweiz. med. Wschr. 1963, 93, 1232, on administration p.o. of from about 0.1 to about 50 mg/kg animal body weight of the compounds.

The compounds are therefore indicated for use as salidiuretic agents. An indicated daily dose is from about 1 to about 500 mg conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 0.2 to about 250 mg of the compounds or in sustained release form.

Additionally, the compounds of formula I exhibit blood-pressure lowering activity as indicated in standard tests, e.g. in the Grollman rat test on administration p.o. and s.c. of from 1 to 10 mg/kg animal body weight of the compounds.

As a result of their activity in the above test and their activity as salidiuretic agents, the compounds are therefore furthermore indicated for use as blood-pressure lowering agents, e.g. for the treatment of high arterial blood pressure. As indicated daily dose is from about 1 to about 100 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 0.25 to about 50 mg of the compounds, or in sustained release form.

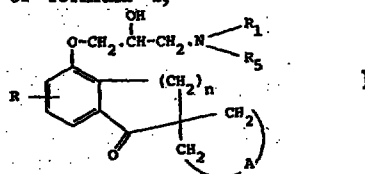
The Example 1 compound exhibits particularly interesting properties.

The compounds may be administered in pharmaceutically acceptable acid addition salt form. Such forms exhibit the same order of activity as the free base forms. The present invention also provides a pharmaceutical composition comprising a compound of formula I in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. Such compositions may be formulated in conventional manner so as to be, for example, a solution or tablet.

In a group of compounds A is conveniently alkylene and conveniently in formula II R_2 is other than alkoxyalkyl or alkylthioalkyl.

WHAT WE CLAIM IS:—

1. A process for the production of a compound of formula I,



wherein

A is straight chain alkylene of 2 to 4



(13)

The compounds of formula I exhibit pharmacological activity in animals. In particular, the compounds of formula I inhibit glycerol release stimulated by isoproterenol in standard tests, e.g. *in vitro* with fat cells of the epididymal fat pads isolated in accordance with the method of M. Rodbell [J. Biol. Chem. 239 (1964), 375-380], in the presence of 10^{-9} to 10^{-7} Molar solution of the compounds.

Alternatively the inhibition of glycerol release may be observed *in vivo* using rats in conventional manner on administration s.c. of from about 0.03 to about 10 mg/kg animal body weight of the compounds.

The compounds are therefore indicated for use in the treatment of the increase of free fatty acid concentration in the blood induced by emotional stress, and also inhibit lipolysis induced by emotional stress, and myocardial infarction induced by emotional stress.

Additionally, the compounds inhibit hyperglycemia induced by emotional stress as indicated by an inhibition of glycogenolysis induced by isoproterenol in standard tests, e.g. *in vivo* in rats in conventional manner on administration s.c. of from about 0.03 to about 10 mg/kg animal body weight of the compounds.

The compounds are therefore indicated for use in the treatment of hyperglycemia induced by emotional stress, e.g. for suppressing of appetite induced by emotional stress.

For these stress indications an indicated daily dose is from about 10 to about 500 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 2 to about 250 mg of the compound or in sustained release form.

Additionally, the compounds exhibit a cardio-vascular adrenergic β -blocking effect as indicated in standard tests. For example, the compounds, at a concentration of from 0.08×10^{-6} to 10×10^{-6} Molar in the spontaneously beating isolated guinea pig atrium, inhibit the positive inotropic and positive chronotropic adrenaline effect. Additionally, the compounds on administration i.v. of from 0.02 mg/kg to 1 mg/kg to the anaesthetized cat inhibit the isoproterenol-induced tachycardia and blood pressure lowering in the infusion cat test.

The compounds are therefore indicated for use as cardio-vascular adrenergic β -blocking agents, e.g. for the prophylaxis and therapy of Angina pectoris, and also as arrhythmics.

In general, the 2(S) optical isomers are more active than the 2(R) optical isomers.

As indicated daily dose is from about 10 to about 500 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 2 to about

250 mg of the compounds or in sustained release form.

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The compounds are therefore indicated for use as salidiuretic agents. An indicated daily dose is from about 1 to about 500 mg conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 0.2 to about 250 mg of the compounds or in sustained release form.

Additionally, the compounds of formula I exhibit blood-pressure lowering activity as indicated in standard tests, e.g. in the Grollman rat test on administration p.o. and s.c. of from 1 to 10 mg/kg animal body weight of the compounds.

As a result of their activity in the above test and their activity as salidiuretic agents, the compounds are therefore furthermore indicated for use as blood-pressure lowering agents, e.g. for the treatment of high arterial blood pressure. As indicated daily dose is from about 1 to about 100 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 0.25 to about 50 mg of the compounds, or in sustained release form.

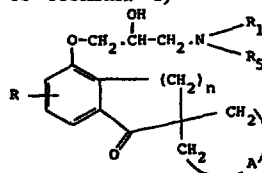
The Example 1 compound exhibits particularly interesting properties.

The compounds may be administered in pharmaceutically acceptable acid addition salt form. Such forms exhibit the same order of activity as the free base forms. The present invention also provides a pharmaceutical composition comprising a compound of formula I in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. Such compositions may be formulated in conventional manner so as to be, for example, a solution or tablet.

In a group of compounds A is conveniently alkylene and conveniently in formula II R_2 is other than alkoxyalkyl or alkylthioalkyl.

WHAT WE CLAIM IS:—

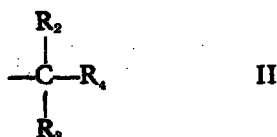
1. A process for the production of a compound of formula I,



wherein

A is straight chain alkylene of 2 to 4

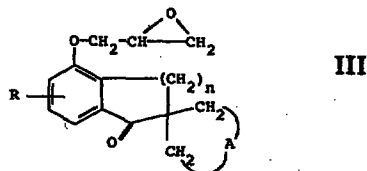
carbon atoms, or straight chain alkenylene of 2 to 4 carbon atoms,
 n is 1, 2 or 3,
 R is hydrogen or halogen of atomic number from 9 to 35, and
 either (i) R_1 is a group of formula II,



wherein

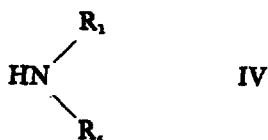
- 10 R_2 and R_3 , independently, are hydrogen or alkyl of 1 to 4 carbon atoms, and
 R_4 is alkyl of 1 to 4 carbon atoms, alkoxy-alkyl of 2 to 5 carbon atoms, alkylthio-alkyl of 2 to 5 carbon atoms, phenyl-alkyl or phenoxyalkyl or phenylthioalkyl,
 15 wherein the alkyl moiety has from 1 to 3 carbon atoms, or phenyl, the phenyl ring of each of the last four radicals being unsubstituted or mono-substituted by, or di-substituted independently by, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, hydroxy or halogen of atomic number from 9 to 35, and
 R_5 is hydrogen,
 or (ii) R_1 and R_5 together with the nitrogen atom to which they are bound are
 25 (a) 2,2,6,6-tetramethylpiperidinyI,
 (b) 2,2,5,5-tetramethylpyrrolidinyI, or
 (c) piperazinyI substituted in the 4 position by alkyl of 1 to 4 carbon atoms or phenyl which is unsubstituted, or mono-substituted by, or di- or tri-substituted independently by, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halogen of atomic number from 9 to 35,

which comprises reacting a compound of formula III,



40 wherein

A, n and R are as defined above, or a reactive functional derivative thereof, with a compound of formula IV,



45 wherein

R_1 and R_5 are as defined above.

2. A process for the production of a compound of formula I, as stated in claim 1, substantially as hereinbefore described with reference to any one of the Examples.

3. A compound of formula I, whenever produced by a process according to claim 1 or 2.

4. A compound of formula I, as defined in claim 1.

5. A compound of claim 4, wherein R is hydrogen.

6. A compound of claim 5, wherein A is straight chain alkylene.

7. A compound of claim 6, wherein R_1 and R_5 are as defined in claim 1 with the proviso that in formula II R_4 is other than alkoxyalkyl or alkylthioalkyl.

8. A compound of claim 5, which is 4'-(3-tert.-butylamino-2-hydroxypropoxy)-spiro(cyclohexane-1,2'-indan)-1'-one.

9. A compound of claim 5, wherein R_5 is hydrogen.

10. A compound of claim 9, wherein R_1 is $-C(CH_3)_3$.

11. A compound of claim 10, wherein n and A are respectively 2 and $-(CH_2)_2-$.

12. A compound of claim 10, wherein n and A are respectively 1 and $-(CH_2)_2-$.

13. A compound of claim 10, wherein n and A are respectively 2 and $-(CH_2)_2-$.

14. A compound of claim 10, wherein n and A are respectively 2 and $-(CH_2)_2-$.

15. A compound of claim 10, wherein n and A are respectively 1 and $-(CH_2)_2-$.

16. A compound of claim 5, wherein R_1 and R_5 together are



17. A compound of claim 16, wherein n and A are respectively 1 and $-(CH_2)_2-$.

18. A compound of any one of claims 3 to 17 in racemic form.

19. A compound of any one of claims 3 to 17 in 2(S) form.

20. A compound of any one of claims 3 to 17 in 2(R) form.

21. A compound of claim 4 in which 2(S) 4'-(3-tert.-butylamino-2-hydroxypropoxy)-spiro(cyclohexane-1,2'-indan)-1'-one.

22. A compound of claim 4 which is 2(R) 4'-(3-tert.-butylamino-2-hydroxypropoxy)-spiro(cyclohexane-1,2'-indan)-1'-one.

23. A compound according to any one of claims 3 to 22 in free base form.

24. A compound according to any one of claims 3 to 22 in acid addition salt form.

25. A pharmaceutical composition comprising a compound of any one of claims 3 to 22 in free base or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.



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