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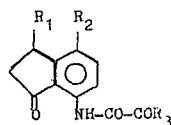
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(54) **Oxaminic acids and esters, process for their preparation and their pharmaceutical use.**

(57) Compounds of the formula:



wherein R_1
is hydrogen or alkyl of 1 to 10 carbon atoms,
 R_2 is chlorine or alkoxy of 1 to 4 carbon atoms, or
 R_1 and R_2 together are $-(CH_2)_m-$
wherein m is 3 or 4

and R_3 is OH or alkoxy of 1 to 4 carbon atoms are prepared.
The compounds are obtained by acylation of the amino
derivative with an oxalic-esters derivative. Hydrolysis of the
oxamic ester gives the oxamic acid.

The compounds are useful for the treatment of allergic
conditions.

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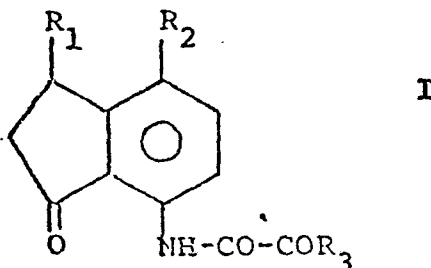
TITLE MODIFIED

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IMPROVEMENTS IN OR RELATING TO ORGANIC COMPOUNDS

This invention relates to oxaminic acids and esters thereof, a process for the preparation of said compounds and pharmaceutical compositions containing these compounds.

5 More particularly, the invention provides compounds of formula I,



wherein R_1 is hydrogen or alkyl of 1 to 10 carbon atoms,

R_2 is chlorine or alkoxy of 1 to 4 carbon atoms, or

R_1 and R_2 together are $-(CH_2)_m-$

10 wherein m is 3 or 4,

and R_3 is OH or alkoxy of 1 to 4 carbon atoms.

When R_1 is alkyl of 1 to 10 carbon atoms, this preferably contains 1 to 5 carbon atoms, especially 2 or 3 carbon atoms. R_1 can also be hydrogen.

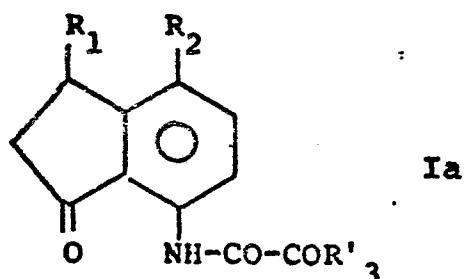
15 R_2 can be chlorine. R_2 can also be alkoxy of 1 to 4 carbon atoms. R_1 and R_2 together can also be $-(CH_2)_m-$ wherein m is 3 or 4, preferably 3.

R_3 can be OH. R_3 can also be alkoxy of 1 to 4 carbon atoms.

20 The invention also provides a process for the production of compounds of formula I comprising,

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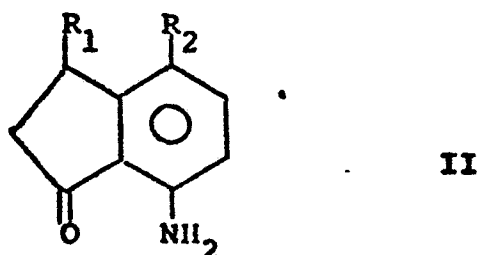
a) producing a compound of formula Ia,



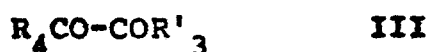
wherein R_1 and R_2 are as previously defined and

R'_3 is alkoxy of 1 to 4 carbon atoms,

by reacting a compound of formula II,



5 wherein R_1 and R_2 are as previously defined,
with a compound of formula III,



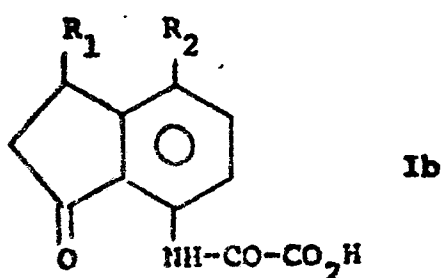
wherein R'_3 is as previously defined and

R_4 is chlorine, bromine, alkoxy of 1 to 4 carbon
atoms, phenoxy, or phenoxy monosubstituted by

10 chlorine, bromine, alkyl of 1 to 4 carbon atoms
or alkoxy of 1 to 4 carbon atoms

or

b) producing a compound of formula Ib,



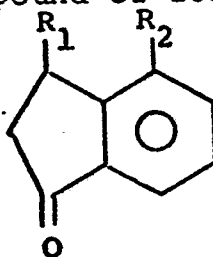
by hydrolysing a compound of formula Ia as hereinbefore defined.

Process variant a) can be effected according to known methods. For example, the reaction may conveniently
5 be effected in the presence of an inert solvent such as a hydrocarbon, chlorinated hydrocarbon, an ether or a tertiary amine, or in an excess of the compound of formula III. The reaction may suitably be effected at a temperature of from -5° to 200°C . A basic catalyst, such as a
10 tertiary amine, for example pyridine or triethylamine may be employed. When R_4 is alkoxy of 1 to 4 carbon atoms, this preferably has the same significance as R_3 .

Process variant b) can be effected according to known methods. The reaction is preferably effected in
15 the presence of a base, for example in the presence of a dilute alkali metal hydroxide or a tertiary amine. The reaction may suitably be effected at a temperature of from 0°C to the boiling temperature of the reaction mixture, conveniently in the presence of an inert organic solvent
20 which is miscible with water, such as a lower alcohol, dimethyl sulphoxide or dimethoxy ethane.

The resulting compounds of formula I may be isolated and purified using conventional techniques. The compounds of formula I wherein R_3 is OH may be converted into salt forms in conventional manner and vice versa. Suitable salt forms include those with alkali metals, for example sodium and potassium, alkaline earth metals, for example calcium and magnesium, and with organic bases such as amines.

The compounds of formula II can be prepared by nitrating a compound of formula IV,



IV

for example in a mixture of sulphuric and nitric acids, and reducing the resulting nitro derivative, according to known methods, to yield the compounds of formula II. The reduction may conveniently be effected by catalytic hydrogenation or by using iron filings in an aqueous acid.

Insofar as the production of the starting materials has not been described, these are either known or may be produced in conventional manner from available materials, or by methods analogous to those described herein.

In the following Examples, all temperatures are in degrees Celsius.

EXAMPLE 1: N-(2,6,7,8,9,9a-hexahydro-2-oxo-1H-
benz[c,d]azulen-3yl)oxaminic acid ethyl ester

A solution of 5.0 g of 2,6,7,8,9,9a-hexahydro-2-oxo-1H-benz[c,d]azulen-3yl-amine in 26 ml of diethyl
5 oxalate is refluxed for 2 hours and then cooled to room
temperature. The reaction mixture is then distilled in
a bulb tube at 90-100°/11 mm to remove the excess of
diethyl oxalate, and the residue is purified by chroma-
tography on 300 g of silica gel. The title compound is
10 recrystallised from ether, m.p. 115-117°.

The 2,6,7,8,9,9a-hexahydro-2-oxo-1H-benz[c,d]-
azulen-3yl-amine employed as starting material can be
prepared as follows:

- a) A solution of 20 g of potassium nitrate in 100 ml of
15 conc. sulphuric acid is added dropwise, with stirring,
to a solution of 36 g of 2,6,7,8,9,9a-hexahydro-1H-benz-
[c,d]-azulen-2-one in 200 ml of conc. sulphuric acid at
5° and then stirred for 1 hour at 0-5°. The reaction
mixture is poured onto ice, extracted with chloroform,
20 the extract washed with water, dried over sodium
sulphate and concentrated. The raw product is dis-
solved in methylene chloride and filtered through
400 g of silica gel. After reducing the volume of the
solvent, raw 2,6,7,8,9,9a-hexahydro-3-nitro-1H-benz-
25 [c,d]azulen-2-one (containing 2,6,7,8,9,9a-hexahydro-4-
nitro-1H-benz[c,d]azulen-2-one) is crystallised from
methanol, m.p. 107-110°.

b) 20 g of 2,6,7,8,9,9a-hexahydro-3-nitro-1H-benz[c,d]-
 azulene-2-one are added to 135 ml of acetic acid and
 6 g of iron filings and 18 ml of water added whilst
 stirring. Further charges of 6 g of iron filings and
 18 ml of water are added over intervals of 15, 30,
 45 and 60 minutes. The mixture is stirred for a fur-
 ther 30 minutes, diluted with 900 ml of water and
 extracted with methylene chloride. After reducing
 the volume of the methylene chloride extract, the
 remaining 2,6,7,8,9,9a-hexahydro-2-oxo-1H-benz[c,d]
 azulene-3-yl-amine is purified by chromatography on
 silica gel. M.p. 135-138°.

The following compounds can be prepared in manner analog-
 ous to that described in Example 1, using appropriate
 starting materials in approximately equivalent amounts.

TABLE 1

Ex. No.	R ₁	R ₂	R ₃	M.P.
2	-(CH ₂) ₃ -		OC ₂ H ₅	85-87°
3	-(CH ₂) ₃ -		OCH ₃	153-155°
4	H	OCH ₃	OC ₂ H ₅	170-172°
5	n-C ₃ H ₇	Cl	OC ₂ H ₅	

EXAMPLE 6: N-(2,6,7,8,9,9a-hexahydro-2-oxo-1H-benz[c,d]-
azulen-3-yl) oxaminic acid

A solution of 0.95 g of potassium hydroxide in
2 ml of water is added to a solution of 4 g of the title
5 compound of Example 1 in 150 ml of methanol and the
mixture refluxed for 1 hour. The solution is concentrated,
diluted with water and the neutral side products extrac-
ted with CH_2Cl_2 . The aqueous phase is acidified with
hydrochloric acid and the title compound filtered off.
10 M.P. 191-192°.

The following compounds can be prepared in manner
analogous to that described in Example 5, using appropri-
ate starting materials in approximately equivalent amounts.

TABLE 2

Ex. No.	R_1	R_2	R_3	M.P.
7	$-(\text{CH}_2)_3-$		OH	208-210°
8	H	$-\text{OCH}_3$	OH	221-223°
9	$n\text{-C}_3\text{H}_7$	Cl	OH	

The compounds of formula I exhibit pharmacological activity. In particular, the compounds exhibit disodium chromoglycate (DSCG)-like activity, in particular histamine release inhibiting activity, and are therefore indicated for use in the treatment and prophylaxis of allergic conditions, such as allergic asthma, exercise induced asthma and allergic gastrointestinal disorders, as indicated in the passive cutaneous anaphylaxis (PCA) test in the rat, based on the principles of Mota, J. Immunology, (1964); 7, 681.

The (DSCG)-like activity, in particular histamine release inhibiting activity, can be confirmed by inhibition of histamine release in the rat peritoneal mast cell test, basically as described by Kusner et al., J. Pharmacol. Exp. Therap. (1973), 184, 41-46.

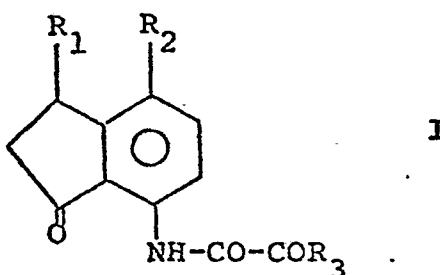
An indicated suitable daily dosage is from about 1 to about 100 mg, suitably administered in divided doses of from about 0.25 to about 50 mg, 2 to 4 times daily or in retard form.

The compounds of formula I wherein R_3 is OH may be administered in free form or in pharmaceutically acceptable salt form. Such salt forms possess the same order of activity as the free forms and are readily prepared in conventional manner. Examples of suitable salt forms are those of sodium and potassium.

The invention also provides a pharmaceutical composition comprising a compound of formula I, and in the case of compounds wherein R_3 is OH, in free form or in pharmaceutically acceptable salt form, 5 in association with a pharmaceutically acceptable diluent or carrier. Such compositions may, for example, be in the form of a solution or capsule.

WHAT WE CLAIM IS:

1. A compound of formula I,



wherein R_1 is hydrogen or alkyl of 1 to 10 carbon atoms,

R_2 is chlorine or alkoxy of 1 to 4 carbon atoms, or

R_1 and R_2 together are $-(CH_2)_m-$
wherein m is 3 or 4

and R_3 is OH or alkoxy of 1 to 4 carbon atoms.

2. A compound of Claim 1, wherein R_1 and R_2
together are $-(CH_2)_3-$.

3. A compound of Claim 1, wherein R_3 is OH.

4. A compound of Claim 1, wherein R_3 is alkoxy
of 1 to 4 carbon atoms.

5. A compound of Claim 3, in salt form.

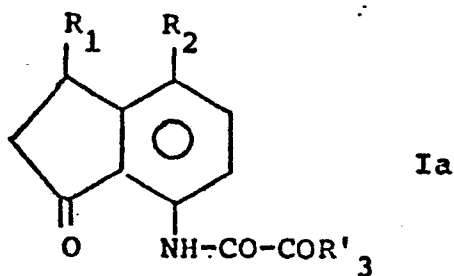
6. A compound of Claim 3, in free form.

7. A compound of Claim 1, wherein R_1 and R_2
together are $-(CH_2)_3-$ and R_3 is OH.

8. A pharmaceutical composition comprising a compound according to any one of Claim 1 to 7, and, in the case of compounds wherein R_3 is OH, in free form or in pharmaceutically acceptable salt form, in association with a pharmaceutically acceptable carrier or diluent.

9. A process for the production of a compound of formula I, as defined in Claim 1, comprising

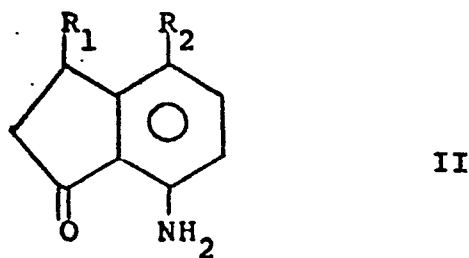
a) producing a compound of formula Ia,



wherein R_1 and R_2 are as previously defined and

R'_3 is alkoxy of 1 to 4 carbon atoms,

by reacting a compound of formula II,



wherein R_1 and R_2 are as previously defined,

with a compound of formula III,



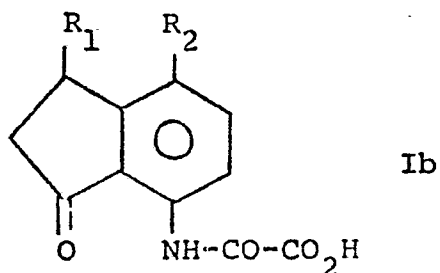
wherein R'_3 is as previously defined and

R_4 is chlorine, bromine, alkoxy of 1 to 4 carbon

atoms, phenoxy, or phenoxy monosubstituted by
chlorine, bromine, alkyl of 1 to 4 carbon atoms
or alkoxy of 1 to 4 carbon atoms,

or

- 5 b) producing a compound of formula Ib,



by hydrolysing a compound of formula Ia, as herein-
before defined.

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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	<u>US - A - 2 589 934</u> (H.J. GLENN) * Example IV *	1	C 07 C 103/42 A 61 K 31/19 A 61 K 31/225 //C 07 C 97/07 C 07 C 79/36
			TECHNICAL FIELDS SEARCHED (Int. Cl.)
			C 07 C 103/42
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
			&: member of the same patent family, corresponding document
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
The Hague	27-09-1978	RAUWELS	