United States Patent [19]

Dusza et al.

[11] **3,855,276**

[45] **Dec. 17, 1974**

[54] **PHENANTHRYL ETHYLIDENE CARBAZIC ACID ESTERS**

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[73] Assignee: **American Cyanamid Company,** Stamford, Conn.

[22] Filed: **Dec. 17, 1973**

[21] Appl. No.: **425,421**

[52] **U.S. Cl.** ..... **260/471 C,** 424/300

[51] **Int. Cl.** **C07c 125/06**

[58] **Field of Search** ..... 260/471 C

[56] **References Cited**

UNITED STATES PATENTS

3,560,503 2/1971 Anand et al. ..... 260/471 C

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Attorney, Agent, or Firm—Ernest Y. Miller

[57] **ABSTRACT**

The preparation of the phenanthryl ethylidene carbazic acid alkyl esters having antirhinoviral activity and method of use are described.

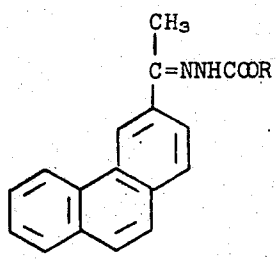
3 Claims, No Drawings

PHENANTHRYL ETHYLIDENE CARBAZIC ACID ESTERS

DESCRIPTION OF THE INVENTION

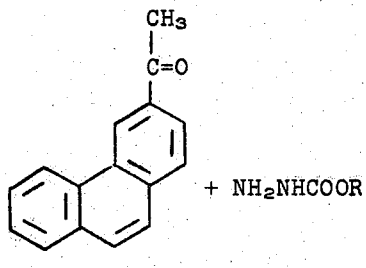
This invention is concerned with phenanthryl ethylidene carbazic acid alkyl esters and method of using the same.

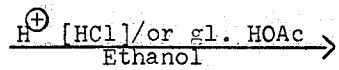
In particular, this invention relates to compounds of the formula:



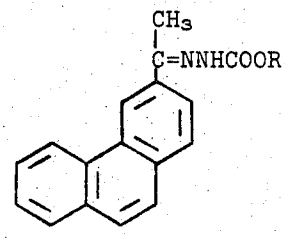
Wherein R is lower alkyl C_1 to C_6.

The compounds of the present invention are prepared by methods which can be graphically illustrated as follows:





1-2 Hrs. Reflux



Wherein R is a lower alkyl, C_1 to C_6.

Among the specific compounds which can be prepared by the above method are, for example: 3-[1-(3-phenanthryl)ethylidene]-carbazic acid ethyl ester, 3-[1-(3-phenanthryl)ethylidene]carbazic acid methyl ester, 3-[1-(3-phenanthryl)ethylidene]-carbazic acid propyl ester, 3-[1-(3-phenanthryl)ethylidene]-carbazic acid t-butyl ester, 3-[1-(3-phenanthryl)ethylidene]-carbazic acid hexyl ester.

The compounds of the present invention exhibit antiviral activity against a variety of rhinoviruses.

The following procedure is used to determine the anti-rhinoviral activity of the present compounds. Confluent monolayers of a continuous cell-line such as HeLa, HEp-2, KB or L-132 grown in plastic tissue culture dishes were infected with one of the viruses causing respiratory illness such as the "common cole." These viruses include members of the picornavirus group including the rhinoviruses, for example, types 1B, 2, 5, 14, or 23 and including the enteroviruses, for example, Coxsackie A-15 or A-21. Protection of the tissues to the cytopathic effects of the viruses was ascertained by means of a plaque inhibition test in which the test compound was adsorbed into a filter paper disc and placed on the agar used to overlay the infected cell monolayers, or by incorporation into the said agar overlay. The agar medium used for this purpose was of the following formulation:

Minimum Essential Medium (Eagles) containing Earle's Salts (Grand Island Biological Company, Grand Island, N.Y.) and to which has been added:

The virus-infected cell monolayers plus test compound were incubated for 3 to 5 days in a humidified atmosphere of 5 percent carbon dioxide at either 33° or 37°C., depending on the virus. The ability of these compounds to protect tissues from destruction by the viruses was then evident after staining the residual, uninfected cells with 0.5 percent crystal violet in 20 percent ethanol.

A summary of the test results obtained on representative compounds are shown in Table I.

In addition, 3-[1-(3-phenanthryl)ethylidene]-carbazic acid ethyl ester is also active in providing protection against Coxsackie A-21 virus.

The active components of this invention can be used in compositions such as tablets; the principal active ingredient is mixed with conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, gums, or similar materials as non-toxic pharmaceutically acceptable diluents or carriers. The tablets or pills of the novel compositions can be laminated or otherwise compounded to provide a dosage form affording the advantage of prolonged or delayed action or predetermined successive action of the enclosed medication. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids or mixtures of polymeric acids with such materials as shellac, shellac and cetyl alcohol, cellulose acetate and the like. A particularly advantageous enteric coating comprises a styrene-maleic acid copolymer together with known materials contributing to the enteric properties of the coating.

The liquid forms in which the novel compositions of the present invention may be incoporated for administration include suitably flavored emulsions with edible oils, such as, cottonseed oil, sesame oil, coconut oil, peanut oil, and the like, as well as elixirs and similar pharmaceutical vehicles. Sterile suspensions or solutions can be prepared for parenteral use. Isotonic prep-

arations containing suitable preservatives are also desirable for injection use.

The term dosage form as described herein refers to physically discrete units suitable as unitary dosage for warmblooded animal subjects, each unit containing a predetermined quantity of active component calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier or vehicle. The specification for the novel dosage forms of this invention are indicated by characteristics of the active component and the particular therapeutic effect to be achieved or the limitations inherent in the art of compounding such an active component for therapeutic use in warm-blooded animals as disclosed in this specification. Examples of suitable oral dosage forms in accord with this invention are tablets, capsules, pills, powder packets, granules, wafers, cachets, teaspoonfuls, dropperfuls, ampules, vials, segregated multiples of any of the foregoing and other forms as herein described.

DETAILED DESCRIPTION

The following examples describe in detail the preparation of representative compounds of this invention.

EXAMPLE 1

Preparation of
3-[1-(3-Phenanthryl)ethylidene]-carbazic acid ethyl ester

A mixture of 4.4 gm. of 3-acetylphenanthrene, 2.1 gm. of ethyl carbazate and 2 drops of concentrated hydrochloric acid in 100 ml. of 95 percent ethanol is heated on a steam bath for 1 hour, cooled to room temperature and then filtered. The precipitate is dissolved in methylene chloride and passed through an acid silicate of magnesium column. The refluxing effluent is treated with hexane to crystallization. The product is collected and dried, yielding 4.0 gm., melting point 164°–165°C. Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.59; H, 5.91; N, 9.11.

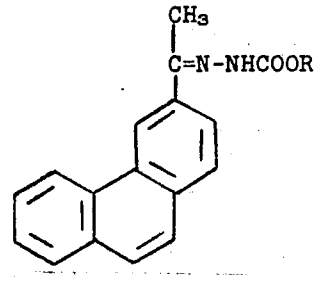
EXAMPLE 2

Preparation of
3-[1-(3-Phenanthryl)ethylidene]-carbazic acid methyl ester

A mixture of 11.0 gm. of 3-acetylphenanthrene and 9.0 gm. of methyl carbazate in 50 ml. of a solution of 4 percent glacial acetic acid in absolute ethanol is refluxed for 2 hours and then cooled in a refrigerator. The precipitate is washed with 95 percent ethanol and then water. The precipitate is dissolved in methylene chloride and passed through an acid silicate of magnesium column. The refluxing effluent is treated with hexane to crystallization. The product is collected and dried, yielding 12.1 gm., melting point 176°–178.5°C. Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.05; H, 5.57; N, 9.55.

We claim:

1. A compound of the formula:



wherein R is lower alkyl C_1 to C_6.

2. The compound in accordance with claim **1**, 3-[1-(3-phenanthryl)ethylidene]-carbazic acid ethyl ester.

3. The compound in accordance with claim **1**, 3-[1-(3-phenanthryl)ethylidene]-carbazic acid methyl ester.

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UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 3,855,276 Dated December 17, 1974

Inventor(s) John Paul Dusza, Harry Lee Lindsay and Seymour Bernstein

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 2, between lines 21 and 22, please insert the following:

-- Ionagar No. 2 ..... 0.4%
Diethylaminoethyl dextran 0.01%
Magnesium chloride 0.06%
Fetal calf serum ..... 2% (v/v) --

Column 2, between lines 31 and 32, please insert the following table:

TABLE I

	Rhinovirus				
	1B	2	5	14	23
3-[1-(3-Phenanthryl)ethylidene]carbazic acid ethyl ester	+	+	+	+	+
3-[1-(3-Phenanthryl)ethylidene]-carbazic acid methyl ester	+	+			+

+ = Protects tissue from destruction by virus.

Signed and sealed this 8th day of April 1975.

(SEAL)
Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents
and Trademarks

FORM PO-1050 (10-69)

USCOMM-DC 60376-P69
* U.S. GOVERNMENT PRINTING OFFICE : 1969 O—366-334