United States Patent Office 3,830,793
Patented Aug. 20, 1974

3,830,793

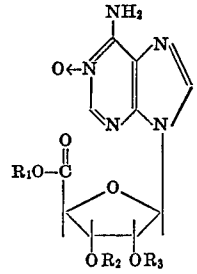
N^1-OXIDES OF ADENOSINE-5'-CARBOXYLATES

Raj Nandan Prasad, Pierrefonds, Quebec, Canada, assignor to Abbott Laboratories, North Chicago, Ill.

No Drawing. Filed Oct. 3, 1972, Ser. No. 294,741
Int. Cl. C07d 51/54
U.S. Cl. 260—211.5 R 10 Claims

ABSTRACT OF THE DISCLOSURE

N^1-Oxides of adenosine-5'-alkyl carboxylates represented by the structural formula



wherein R_1 is loweralkyl, lowerhydroxyalkyl or lowerhaloalkyl, and R_2 and R_3 each are hydrogen or acyl or when taken together form an isopropylidene or a benzylidene moiety, and the pharmaceutically acceptable acid addition salts thereof. The compounds are useful as anti-anginal agents.

BACKGROUND OF THE INVENTION

Angina pectoris is a coronary syndrome characterized by a special type of paroxysmal sensation of pressing or strangling pain usually located behind the sternum or in the precordial region. The pain often radiates to the back of the left arm but may often radiate elsewhere. The attacks can vary greatly in severity and frequency.

Generally speaking, anginal pain rises from an imbalance in the heart between the supply of and the demand for oxygen. The pain is usually brought about by episodes of extreme emotional stress, exposure to cold, excitement or any other stressful situation. In summation, any sudden increase in cardiac work, any decrease in coronary blood flow or any interference with oxygenation of the blood may cause an attack. However, anginal attacks can occur while the patient is sleeping. Therefore, anginal pain is not necessarily due to a decrease of blood flow but rather to an insufficiency of the flow in relation to the metabolic requirements or oxygen demands of the heart.

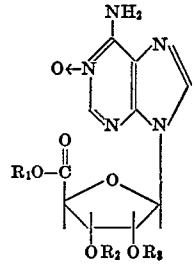
There are several available drugs useful in the management of angina pectoris attacks. Most of the therapeutic agents, such as nitroglycerin and related nitrates are coronary dilators which do not effect the underlying coronary artery pathology or myocardial cardiac damage. Accordingly, currently available therapy is symptomatic rather than curative. Nitroglycerin is probably the most widely used agent in managing acute attacks of angina; however, there has been a long standing need for a prophylactic agent which, when administered to patients with a history of, or who are susceptible to attacks of angina pectoris, will prevent or reduce the severity of future attacks.

The present invention provides a novel class of compounds which are orally active, long-acting anti-anginal agents.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to N^1-oxides of adenosine-5'-alkyl carboxylates, to therapeutic compositions containing such compounds as the active ingredient, to methods of making and using the compounds and to intermediates useful in the preparation of the compounds.

The compounds of this invention are represented by the structural formula



wherein R_1 is loweralkyl, lowerhydroxyalkyl or lowerhaloalkyl, and R_2 and R_3 each are hydrogen or acyl or when taken together form an isopropylidene or a benzylidene moiety, and the pharmaceutically acceptable acid addition salts thereof. The compounds are useful as anti-anginal agents.

The term "loweralkyl," as used herein, refers to both straight and branched chain alkyl groups containing from 1 to 6 carbon atoms including methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *neo*-pentyl, *n*-hexyl, and the like.

The term "halo" refers to chloro, bromo, fluoro or iodo.

The terms "lowerhydroxyalkyl" and "lowerhaloalkyl" refer to the above defined C_1–C_6 alkyl groups substituted with a hydroxy or a halo radical.

The term "pharmaceutically acceptable acid addition salts" refers to salts prepared by reacting the ester with an organic or inorganic acid. Representative salts include hydrochloride, hydrobromide, sulfate, bisulfate, acetate, valerate, oleate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, succinate, tartrate, napsylate and the like.

The term "acyl" refers to acetyl, propionyl, butyryl, and the like.

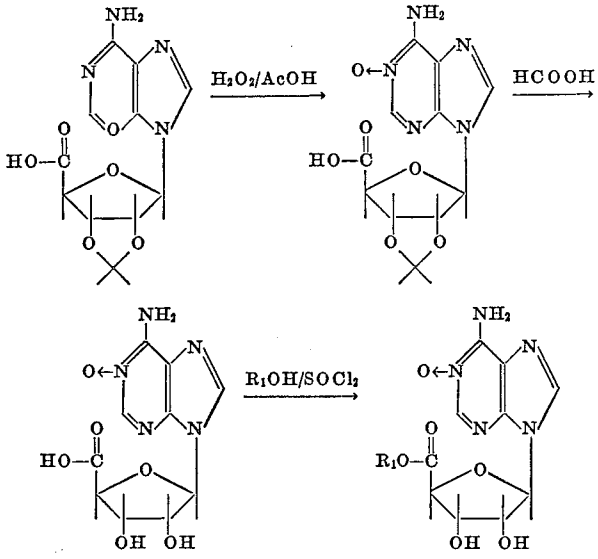
Compounds of this invention wherein R_2 and R_3 are hydrogen are useful as anti-anginal agents at dosages of 0.025 to 30 mg./kg. of body weight daily. The compounds can be administered to angina pectoris patients by either oral or parenteral routes, however the oral route of administration is preferred. While the compounds can be administered in a single dose, it is preferred to administer them in divided dosages, i.e., three to four times daily.

The anti-anginal activity of the compounds of this invention was first established using the method of Schoepke et al., *Pharmacologist 8*: 204 (1966).

Compounds of this invention wherein R_2 and R_3 are acyl or when taken together form an isopropylidene or benzylidene moiety are useful as intermediates for preparing compounds wherein R_2 and R_3 are hydrogen.

The compounds of this invention can be prepared by

forming the N^1-oxide of 2',3'-isopropylidene adenosine carboxylic acid, cleaving the 2',3'-isopropylidene group to obtain the N^1-oxide of adenosine-5'-carboxylic acid, and reacting the acid with the appropriate alcohol (R_1OH) in the presence of, for example, thionyl chloride to obtain the desired product. The reaction is represented by the following reaction sequence.



The following examples further illustrate this invention.

Example 1.—Adenosine-5'-carboxylic acid-N^1-oxide

A suspension of 2',3'-O-isopropylidene adenosine-5'-carboxylic acid [Harmon et al., *Chem. & Ind.*, 114 (1969)] (9.6 g., 0.03 mole) in acetic acid (750 ml.) and H_2O_2 (100 ml. of 30% aqueous solution) was stirred at the room temperature. After 7 days, the reaction mixture was filtered to remove a small amount of suspended material (0.2 g.). The filtrate was cooled to 10–15° C. and the excess of H_2O_2 was destroyed by adding 5% Pd/C (6 g.). The dark mixture was filtered, concentrated under reduced pressure to 75 ml. and poured on to stirred ether (200 ml.). The gray solid was recrystallized from water to give 3.6 g. (dried at 120° C./6 hrs.) of adenosine-5'-carboxylic acid-N^1-oxide, m.p. 220° (dec.) contaminated with traces of 2',3'-O-isopropylidene adenosine-5'-carboxylic acid-N^1-oxide. This material was found to be suitable for the synthesis of its derivatives.

To obtain the pure acid, a small amount (0.84 g.) of the above acid was taken up in 35 ml. of 50% formic acid. After 3 days at room temperature, the clear solution was evaporated under reduced pressure to dryness. The residue was triturated several times with methanol and filtered, and the residue (0.5 g.) was recrystallized from water to give analytically pure adenosine-5'-carboxylic acid-N^1-oxide, m.p. 220° (dec). The structure was confirmed by NMR.

Anal.—Calcd. for $C_{10}H_{11}N_5O_6$: C, 40.40; H, 3.71; N, 23.56; O, 32.32. Found: C, 40.44; H, 3.76; N, 23.84; O, 32.68.

Example 2.—Adenosine-5'-(ethyl)carboxylate-N^1-oxide

Thionyl chloride (2 ml.) was added dropwise to a suspension of adenosine-5'-carboxylic acid-N^1-oxide (1.8 g., 0.006 mole) in absolute ethanol (100 ml.) at 5–10° C. After 30 minutes at 5–10° C., the clear solution was stirred for 16 hours at the room temperature. At the end of this period, the mixture was kept at 50° C. for ½ hour, concentrated under reduced pressure to approximately 20 ml. and poured onto stirred ether (150 ml.). The precipitate was filtered and the residue was stirred with aqueous $NaHCO_3$ (20 ml.) at 10–15° C. and filtered to give 0.8 g. (45%) of the desired product, m.p. 197–200° C. Recrystallization from absolute ethanol gave the analytical sample as a semi-hydrate, m.p. 204–206° C., $[\alpha]_D^{26}$, −22°+2.0° (C.=0.65 in 1N HCl). Infrared and NMR spectra confirmed the structure.

Anal.—Calcd. for $C_{12}H_{15}N_5O_6 \cdot 1/2\ H_2O$: C, 43.11; H, 4.78; N, 20.95. Found: C, 42.84; H, 4.64; N, 20.72.

Examples 3–11

The following compounds are prepared following the procedure of Example 2 by replacing ethanol with the appropriate alcohol.

Adenosine-5' - (chloroethyl)carboxylate - N^1 - oxide, using chloroethyl alcohol.

Adenosine - 5' - (hydroxyethyl)carboxylate - N^1-oxide, using hydroxyethyl alcohol.

Adenosine - 5' - (*n*-propyl)carboxylate - N^1-oxide, using *n*-propanol.

Adenosine - 5' - (*iso*-butyl)carboxylate - N^1 - oxide, using *iso*-butyl alcohol.

Adenosine - 5' - (*n*-butyl)carboxylate-N^1 - oxide, using *n*-butanol.

Adenosine - 5' - (methyl)carboxylate - N^1-oxide, using methanol.

Adenosine - 5' - (*iso*-butyl)carboxylate - N^1 - oxide, using iodomethyl alcohol.

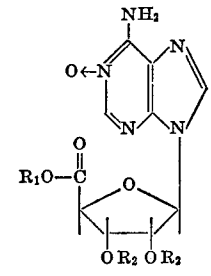
Adenosine - 5' - (*n*-pentyl)carboxylate-N^1-oxide, using pentanol.

Adenosine - 5' - (*n*-hexyl)carboxylate-N^1-oxide, using hexanol.

The compounds of this invention can be formulated into various pharmaceutical dosage forms such as tablets, capsules, pills and the like, for immediate or sustained release, by combining the active compound with suitable pharmaceutically acceptable carriers or diluents according to methods well known in the art. Such dosage forms may additionally include excipients, binders, fillers, flavoring and sweetening agents and other thereapeutically inert ingredients necessary in the formulation of the desired pharmaceutical preparation.

I claim:

1. A compound represented by the formula



wherein R_1 is loweralkyl, lowerhydroxyalkyl or lowerhaloalkyl, and R_2 and R_3 each are hydrogen, acetyl, propionyl, or butyryl, or when taken together form an isopropylidene or benzylidene moiety; or a pharmaceutically acceptable acid addition salt thereof.

2. A compound in accordance with Claim 1 wherein R_2 and R_3 each are hydrogen, or a pharmaceutically acceptable acid addition salt thereof.

3. A compound in accordance with Claim 2 wherein R^1 is loweralkyl, or a pharmaceutically acceptable acid addition salt thereof.

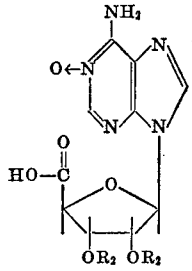
4. A compound in accordance with Claim 3, adenosine - 5' - (ethyl)carboxylate-N^1-oxide, or a pharmaceutically acceptable acid addition salt thereof.

5. A compound in accordance with Claim 1 wherein 5'-(ethyl)carboxylate - N^1 - oxide, hydrochloride.

6. A compound in accordance with Claim 1 wherein R_2 and R_3 are acetyl, propionyl or butyryl.

7. A compound in accordance with Claim 1 wherein R_2 and R_3 taken together form an isopropylidene or benzylidene moiety.

8. A compound represented by the formula



wherein R_2 nd R_3 each are hydrogen, acetyl, propionyl, or butyryl, or when taken together form an isopropylidene or benzylidene moiety.

9. A compound in accordance with Claim 8, 2',3'-isopropylidene adenosine - 5' - carboxylic acid-N^1-oxide.

10. A compound in accordance with Claim 8, adenosine-5'-carboxylic acid-N^1-oxide.

References Cited

UNITED STATES PATENTS

3,317,511	5/1967	Kawashima et al.	260—211.5 R
3,697,504	10/1972	Schmidt	260—211.5 R

JOHNNIE R. BROWN, Primary Examiner

U.S. Cl. X.R.

424—180

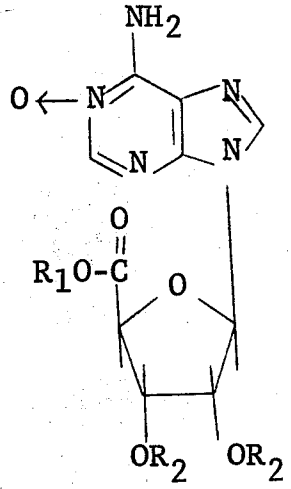
UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,830,793 Dated August 20, 1974

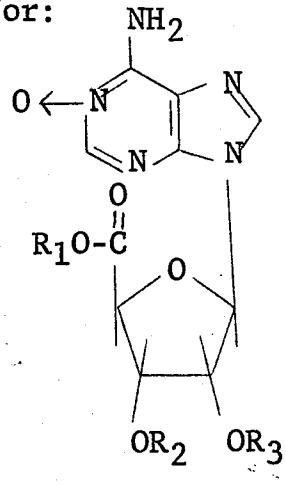
Inventor(s) Raj Nandan Prasad

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

In Column 4, Claim 1, delete the formula :



and substitute therefor:



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

UNITED STATES PATENT OFFICE

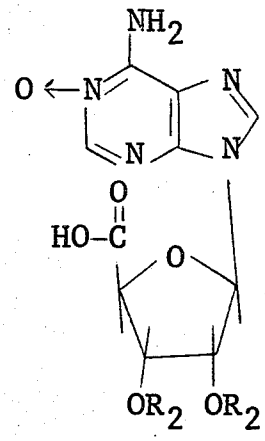
CERTIFICATE OF CORRECTION

Patent No. 3,830,793 Dated August 20, 1974

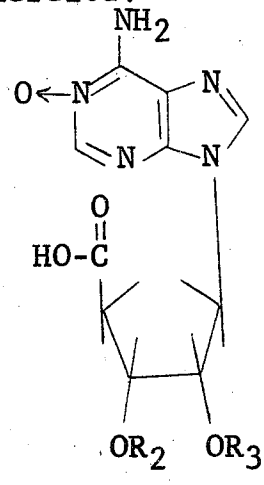
Inventor(s) Raj Nandan Prasad

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

In Column 5, Claim 8, delete the formula:



and substitute therefor:



Signed and sealed this 28th day of January 1975.

(SEAL)
Attest:

McCOY M. GIBSON JR.
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents